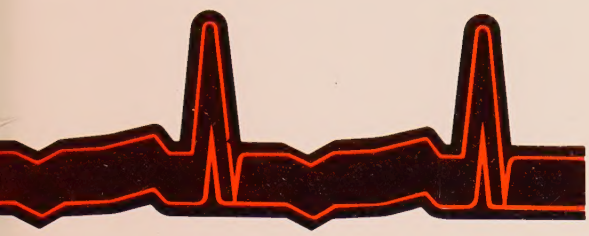
Eighth Report of the Director

National Heart, Lung, and Blood Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • National Institutes of Health

A Symbol of Life . . .

The wave-like drawing on the cover is a stylized representation of an electrocardiogram, a graphic tracing of the electric current produced when the heart muscle is excited. Indeed, the beating heart—pushing oxygen-starved blood through the lungs, and oxygen-rich blood to all body organs and tissues—symbolizes life itself. From this perspective, the National Heart, Lung, and Blood Institute is dedicated to improving our basic knowledge of the workings of the heart, lungs, and blood—individually and as a coordinated whole—so that their disorders can be cured, controlled, and ultimately prevented.



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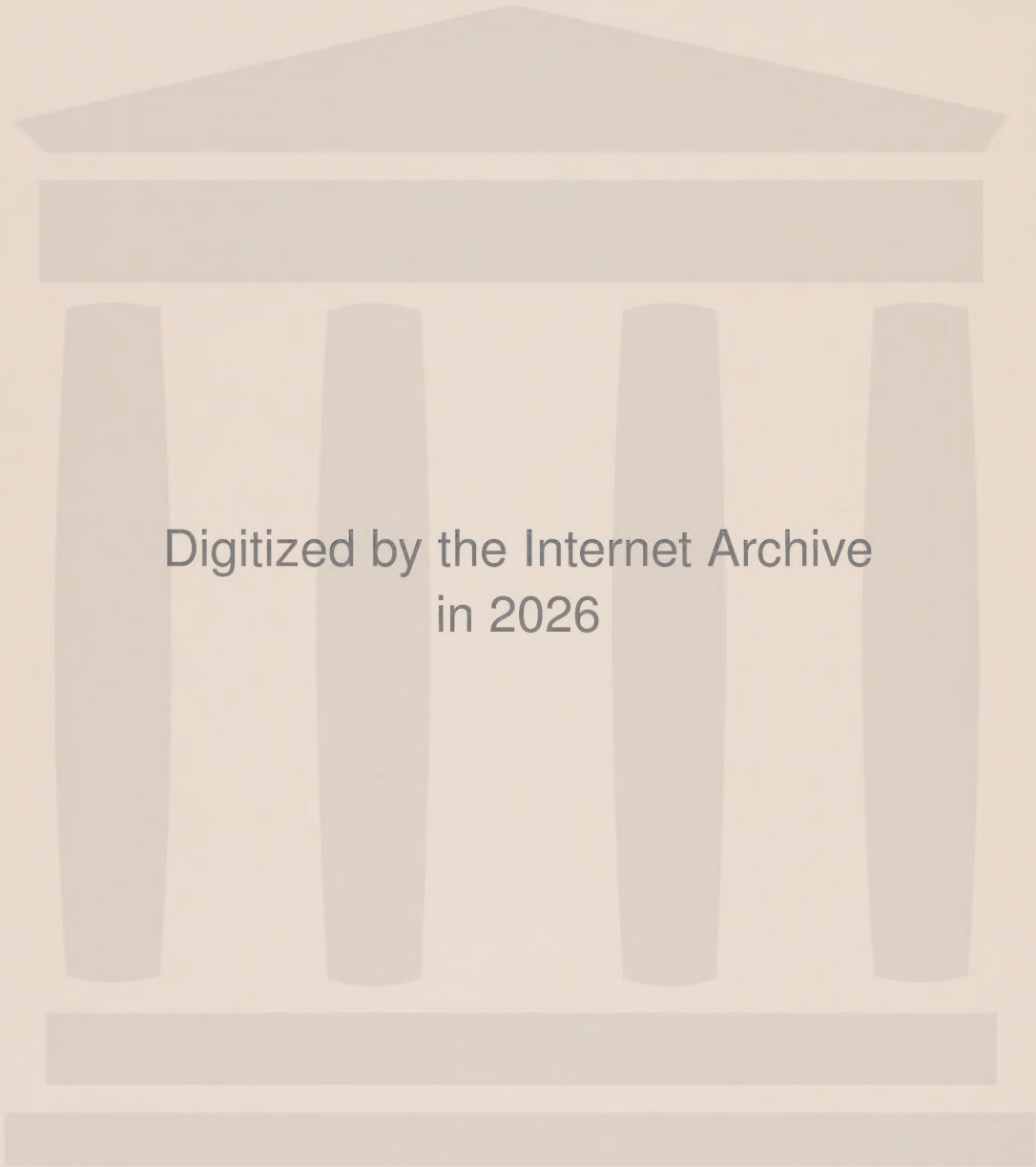
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20205

March 6, 1981

The Honorable Richard S. Schweiker
Secretary of Health and Human Services
Washington, D.C. 20201

Dear Mr. Secretary:

It is with great pleasure that I submit to you the Eighth Report of the Director, National Heart, Lung, and Blood Institute. This volume describes our programs and progress during 1980 and outlines our plans for 1981 through 1985.

Research projects conducted and supported by the Institute have continued to be significant and wide-ranging. Scientific and medical investigators have made important new findings that have contributed to the steady progress we can report again this year. Diseases of the heart, lung, and blood continue to exact a toll in American lives, but the quiet, yet unmistakable advances that continue to accrue are proving responsible for considerable relief. For example, the precipitous decline in deaths from cardiovascular disease seen in the American population since 1970 is being sustained. Contributions from the complete spectrum of biomedical research -- from basic science to prevention, education and control activities -- are having a profound impact on all of the 20 disease-specific program areas that remain the concern of the NHLBI.

Certainly, much remains to be done in our efforts to prevent, control, and treat these diseases as well as to provide for efficacious management of the nation's blood resources. The accomplishments of the past year, however, provide real promise for even greater gains in the years to come. Despite the magnitude of the challenge, the NHLBI continues to take pride in the substantial improvements it has been able to achieve.

Sincerely,

Robert I. Levy

Robert I. Levy, M.D.
Director

Preface

Every 30 seconds, someone in the United States dies from cardiovascular, pulmonary, or blood disease. Every day, countless others endure suffering, disability, and financial loss from the same illnesses. To reduce this grim burden on the American people, the National Heart, Blood Vessel, Lung, and Blood Act of 1972 directed the former National Heart Institute—now the National Heart, Lung, and Blood Institute (NHLBI)—to plan and implement a coordinated national program of research to combat these diseases.

In this volume, *Eighth Report of the Director of the National Heart, Lung, and Blood Institute,* the Institute reports its accomplishments during the past year and projects future needs and goals. In doing so, the report serves as the NHLBI's 1980 update of its Congressionally mandated 5-year National Program Plan. Included are an examination of the dimensions of the challenge facing NHLBI and the Institute's strategy and research programs aimed at responding to that challenge. Selected accomplishments and highlights of 1980 research projects are presented, as are descriptions of 1980 accomplishments of special NHLBI initiatives such as the Specialized Centers of Research program and clinical trials. Activities of major working groups and programs in technology transfer, interagency coordination, international cooperation, and manpower development are described as well. Individual sections set forth goals and planned activities for 1982 through 1986 and the fiscal and personnel requirements to carry out these activities.

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1

Responding to the Challenge:

The Institute's Commitment

Heart, Lung, and Blood Diseases: Taking a Staggering Toll

It is virtually impossible to overstate the magnitude of the problem assumed by the NHLBI in implementing its Congressionally mandated roles: coordination of research in heart, blood vessel, lung, and blood diseases in the United States, and management of our Nation's blood resources.

- At least 40 million Americans have diseases of the heart and blood vessels. Together cardiovascular diseases rank *first* in causes of death, limitation of activity, short-stay hospital discharges and days, and disabled worker benefits; second in physician visits and days of bed disability; and third in lost workdays.
- Respiratory diseases rank first in terms of days of bed disability. More people seek the attention of a physician for respiratory disorders than for any other reason, accounting for 14 percent of all physician office contacts and 8 percent of all short-term hospital stays. Respiratory illness also accounts for more lost workdays than any other category of sickness, totaling more than 135 million days in 1972.
- Although the number of deaths specifically attributable to blood diseases is smaller than that for heart and lung disorders, blood-related problems have a vast adverse impact on disorders in all parts of the body: stroke, myocardial infarction, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, drug toxicity, mismatched blood transfusion, liver disease, and nephritis. As a specific example, nearly 50,000 black Americans suffer from the life-threatening and often crippling disease of sickle cell anemia, an inherited disorder also marked by painful episodes known as "crises."
- The collection, processing, distribution, and proper use of more than 12 million units of blood each year are vital to the provision of modern health care. One of the largest single demands on this resource are the needs of the 20,000 to 25,000 Americans afflicted with hemophilia, 15,000 of them severely enough to require lifelong treatment with costly preparations obtainable only from human blood plasma.

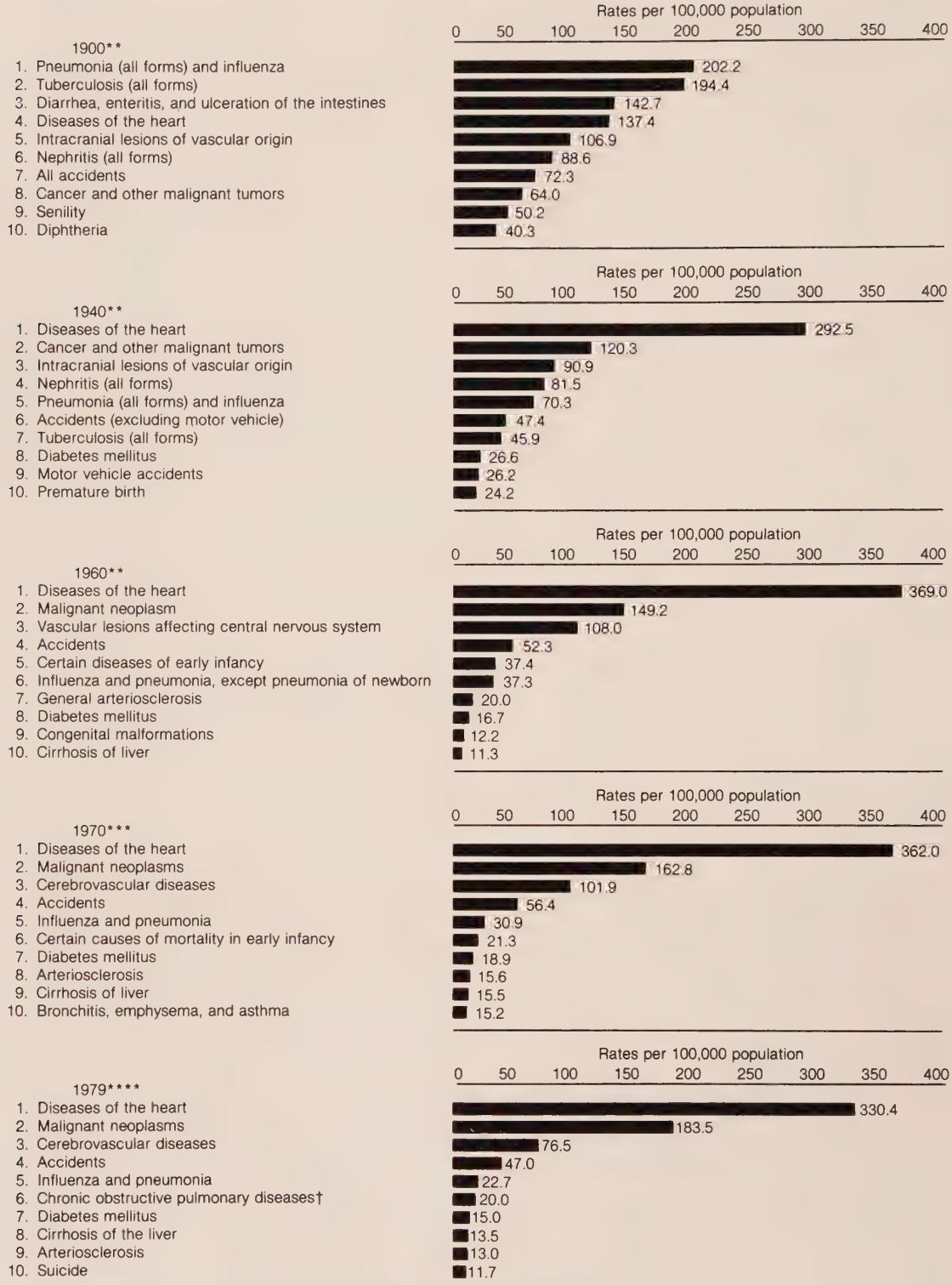
Significantly, 4 of the 10 leading causes of death among Americans in 1979 were conditions that are the concern of the NHLBI: diseases of the heart (ranked first), cerebrovascular diseases (third), chronic obstructive lung disease (fifth), and arteriosclerosis (ninth)—which combined caused nearly 1 million deaths (table 1).

However, the urgent need for research into these diseases was less apparent at the turn of the century. In America in 1900, infectious processes such as pneumonia, influenza, and tuberculosis reigned as our major health problems (figure 1). As these disorders were beginning to come under control, cardiovascular disease (especially that of the coronary arteries) became more prevalent and virulent, raising the specter in the late 1940's and the 1950's of an "epidemic" of cardiovascular disease and accounting for 55.1 percent of all deaths in 1962.

Over the last 30 years, however, this trend has gradually reversed; age-adjusted cardiovascular death rates have been declining slowly since 1950 and then more sharply since 1963. In total, since 1960, age-adjusted cardiovascular death rates have decreased 33 percent compared to only 10 percent for all other causes of death (figure 2).

Most significantly, the decline in coronary and cerebrovascular disease mortality rates has been even more precipitous since 1970 (provisional stroke rates down 36 percent and provisional coronary rates down 24 percent between 1970 and 1979). It has been so sharp, in fact, that in 1975—despite both a growing and aging U.S. population—cardiovascular disease accounted for fewer than 1 million deaths for the first time in a decade. Impressively, if the cardiovascular death rates of 1968 had remained unchanged over the past 10 years, in 1979 alone there would have

Figure 1.
Ten Leading Causes of Death* Among Americans in 1900, 1940, 1960, 1970, and 1979


Rates per 100,000 population
0 50 100 150 200 250 300 350 400
1900**
1. Pneumonia (all forms) and influenza 202.2
2. Tuberculosis (all forms) 194.4
3. Diarrhea, enteritis, and ulceration of the intestines 142.7
4. Diseases of the heart 137.4
5. Intracranial lesions of vascular origin 106.9
6. Nephritis (all forms) 88.6
7. All accidents 72.3
8. Cancer and other malignant tumors 64.0
9. Senility 50.2
10. Diphtheria 40.3
Rates per 100,000 population
0 50 100 150 200 250 300 350 400
1940**
1. Diseases of the heart 292.5
2. Cancer and other malignant tumors 120.3
3. Intracranial lesions of vascular origin 90.9
4. Nephritis (all forms) 81.5
5. Pneumonia (all forms) and influenza 70.3
6. Accidents (excluding motor vehicle) 47.4
7. Tuberculosis (all forms) 45.9
8. Diabetes mellitus 26.6
9. Motor vehicle accidents 26.2
10. Premature birth 24.2
Rates per 100,000 population
0 50 100 150 200 250 300 350 400
1960**
1. Diseases of the heart 369.0
2. Malignant neoplasm 149.2
3. Vascular lesions affecting central nervous system 108.0
4. Accidents 52.3
5. Certain diseases of early infancy 37.4
6. Influenza and pneumonia, except pneumonia of newborn 37.3
7. General arteriosclerosis 20.0
8. Diabetes mellitus 16.7
9. Congenital malformations 12.2
10. Cirrhosis of liver 11.3
Rates per 100,000 population
0 50 100 150 200 250 300 350 400
1970***
1. Diseases of the heart 362.0
2. Malignant neoplasms 162.8
3. Cerebrovascular diseases 101.9
4. Accidents 56.4
5. Influenza and pneumonia 30.9
6. Certain causes of mortality in early infancy 21.3
7. Diabetes mellitus 18.9
8. Arteriosclerosis 15.6
9. Cirrhosis of liver 15.5
10. Bronchitis, emphysema, and asthma 15.2
Rates per 100,000 population
0 50 100 150 200 250 300 350 400
1979****
1. Diseases of the heart 330.4
2. Malignant neoplasms 183.5
3. Cerebrovascular diseases 76.5
4. Accidents 47.0
5. Influenza and pneumonia 22.7
6. Chronic obstructive pulmonary diseases† 20.0
7. Diabetes mellitus 15.0
8. Cirrhosis of the liver 13.5
9. Arteriosclerosis 13.0
10. Suicide 11.7

*Terminology is that used in the edition of International List of Causes of Death in effect at that time.

**SOURCE: *Vital Statistics Rates in the United States 1900, 1960*, National Center for Health Statistics, PHS Pub. No. 1677.

***SOURCE: *Monthly Vital Statistics Report*, Vol. 22, No. 11 (Feb. 22, 1974), NCHS.

****SOURCE: Provisional Statistics, *Monthly Vital Statistics Reports*, Vol. 29, No. 1 (April 9, 1980), NCHS.

† This category supplants "Bronchitis, Emphysema, or Asthma" and anticipates the use of "Chronic obstructive pulmonary diseases" in the ninth revision of the *International Classification of Diseases*, due to current increase in use on death certificates of the term "COPD" rather than a specific disease term.

Table 1.
Mortality from the 10 Leading Causes of Death, United States, 1979*

Cause of Death	Number	Rate per 100,000 Population	Percent
Total	1,895,380	866.2	100.0
1. Heart disease	723,100	330.4	38.2
2. Malignant neoplasms	401,450	183.5	21.2
3. Cerebrovascular diseases	167,320	76.5	8.8
4. Accidents	102,740	47.0	5.4
5. Chronic obstructive pulmonary disease	49,580	22.7	2.6
6. Influenza and pneumonia	43,770	20.0	2.3
7. Diabetes	32,780	15.0	1.7
8. Cirrhosis of the liver	29,620	13.5	1.6
9. Atherosclerosis	28,410	13.0	1.5
10. Suicides	25,710	11.7	1.4
All other causes	290,900	132.9	15.3

*Based on a 10 percent sample of death certificates for the 12 months of 1979. Causes of death were coded to the ninth revision of the *International Classification of Diseases.*

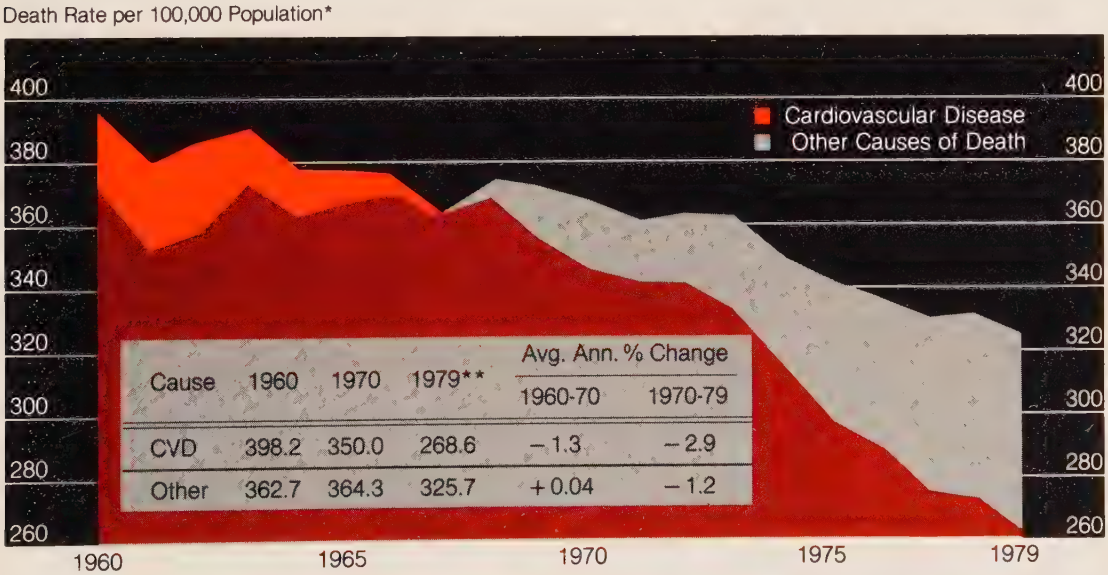
SOURCE: *Monthly Vital Statistics Report,* Vol. 29, No. 1 (April 9, 1980) NCHS.

been 375,000 more cardiovascular deaths than the number that actually occurred.

The downward trends in heart disease mortality can also be illustrated by an examination of the causes of death in two age brackets, as shown in figure 3. Among the leading causes of death at ages 25 to 44, heart disease, which was number one as recently as 1960, dropped to number three in 1978. Similarly, its lead as the number one cause of death at ages 45 to 54 has diminished remarkedly.

It is hard to attribute the ebb and flow in cardiovascular sickness and death to specific events. Clearly, the two major etiologic processes damaging both the heart and blood vessels are hypertension and atherosclerosis. It is because of their

Figure 2.
Death Rates for Cardiovascular Diseases and Other Causes of Death, United States, 1960 to 1979



*Age-adjusted to U.S. population, 1940.

**Estimated by NHLBI.

SOURCE: Prepared by NHLBI. Data from the National Center for Health Statistics.

silent nature that these insidious processes did not receive more attention earlier. Because of their untimely devastating effects on the cardiovascular system, they are now the major subject of research in cardiovascular diseases. In parallel, cardiovascular physiologists have sought to develop better methods to diagnose abnormalities of the blood vessels, heart muscle, and heart valves long before signs or symptoms appear. And during the past 30 years, cardiovascular epidemiologists have also made important contributions by defining risk factors, traits or habits in individuals that identify them as being at increased risk for specific cardiovascular diseases.

A number of major and minor cardiovascular risk factors have been enumerated. They include as major factors age, male sex, hypertension, cigarette smoking, plasma cholesterol levels, and blood glucose; and as lesser factors, overweight, sedentary way of life, softness of water, family history of heart disease before age 65, personality type, and stress.

There is little doubt of the predictive power of the major risk factors, shown graphically in figure 4; two out of every three coronary events (myocardial infarction, coronary death, and coronary insufficiency) occur in high-risk subjects.

The striking association between the currently waning "epidemic" in heart and blood vessel diseases with clear evidence of changing American lifestyles and habits is very hopeful and augers a bright future for preventive cardiology. For example, there has been a decrease in the use of tobacco products, a decrease in the consumption of high saturated fat-high cholesterol foods, and a greater awareness of the need to control both hypertension and obesity and of the potential benefits of exercise.

Despite these encouraging trends, cardiovascular disease remains a problem of staggering proportions, causing over 50 percent of all deaths, about 968,000 in 1979 (figure 5). More than 200,000 of these deaths occur before age 65. Moreover, patients suffering from cardiovascular diseases accounted for more than 49 million days of hospital stay and 55 million physician office visits in 1978 (table 2).

Figure 3.
Number of Deaths from the Three Leading Causes of Death (Ages 25-44 and 45-54) in the United States in 1940, 1950, 1960, 1970, and 1978

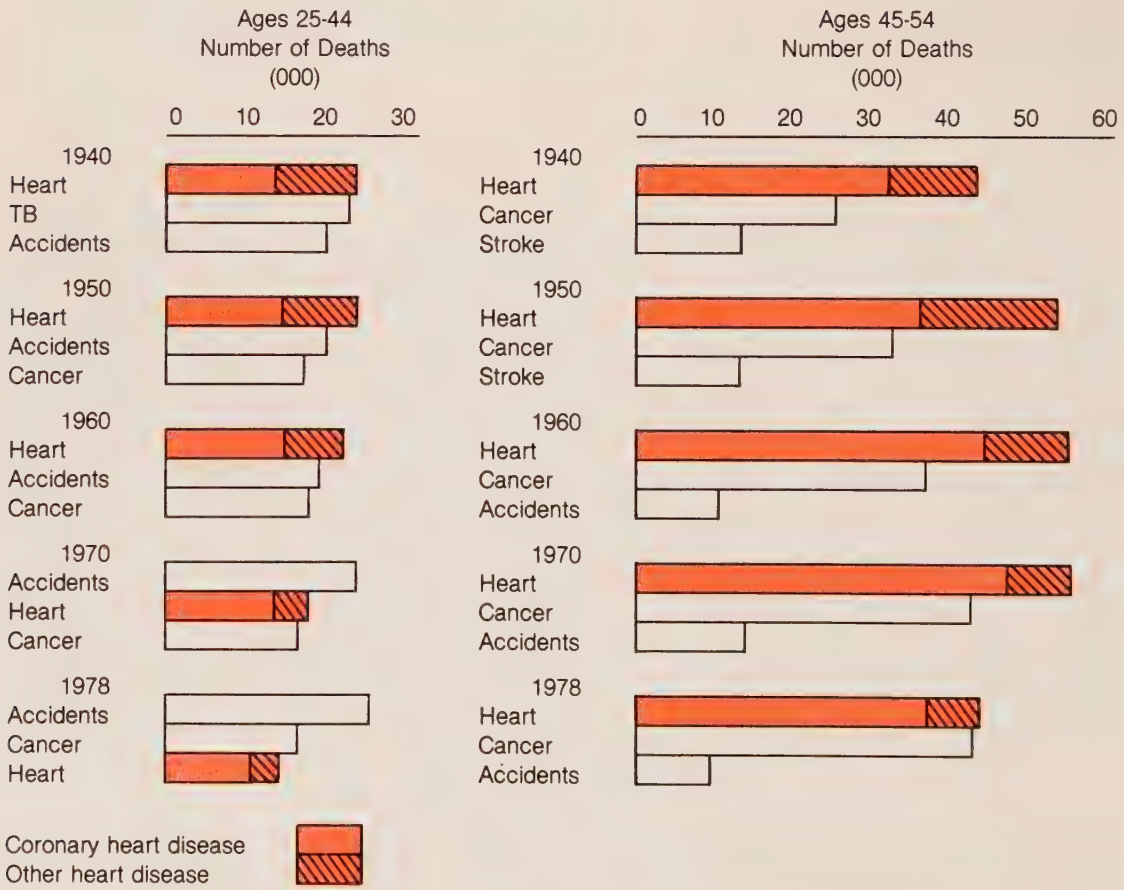
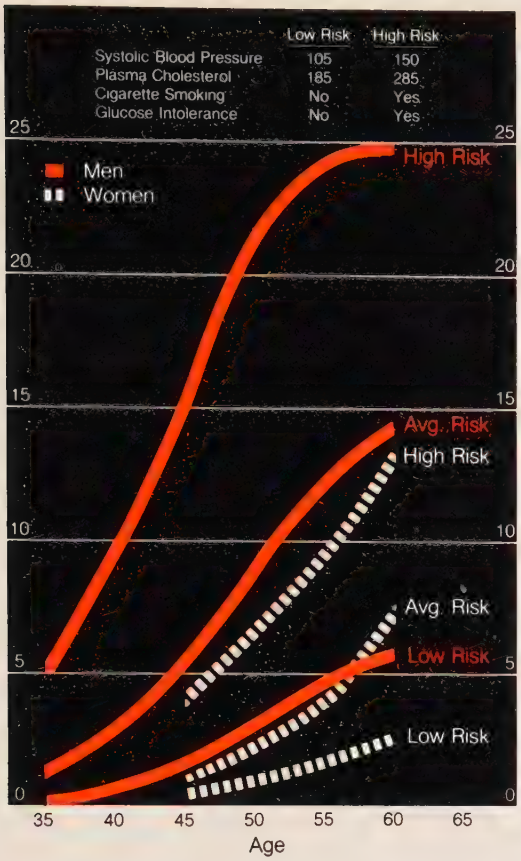


Figure 4.
Coronary Heart Disease Probability*



*Probability of developing coronary heart disease (CHD) in eight years by age, sex, and risk category. (From Feinleib, M.: Am. J. Epidemiol., 104:457, 1976.)

In terms of economic costs, cardiovascular diseases rank first among all medical disorders, totaling more than $60 billion in 1977. Of this amount, $20 billion represents health expenditures, $10 billion productivity lost due to illness, and $30 billion potential productivity lost due to early death. Table 3 summarizes data concerning the economic cost of heart, lung, and blood diseases for year 1975.

Despite the usefulness of these and other indexes in assessing the magnitude of the problem confronting the NHLBI, the overall toll exacted by heart, lung, and blood diseases is immeasurable. The Nation's economic burden of costs associated with mortality and morbidity is perhaps dwarfed by the personal costs of suffering, grief, and loss from these diseases. The following data, illustrating the impact of four selected diseases that are of particular concern to Institute investigators, should be viewed from this perspective.

Coronary Heart Disease

Coronary heart disease, the predominant form of heart disease, is the number one killer in the United States. It is responsible for more than one-third of all deaths and continues to be the most prominent cause of early disability in the American labor force. Coronary heart disease causes chronic illness in about 5 million persons, over half of whom are below age 65. The disease is second only to arthritis in limitation of activity and second only to cancer in total hospital bed days.

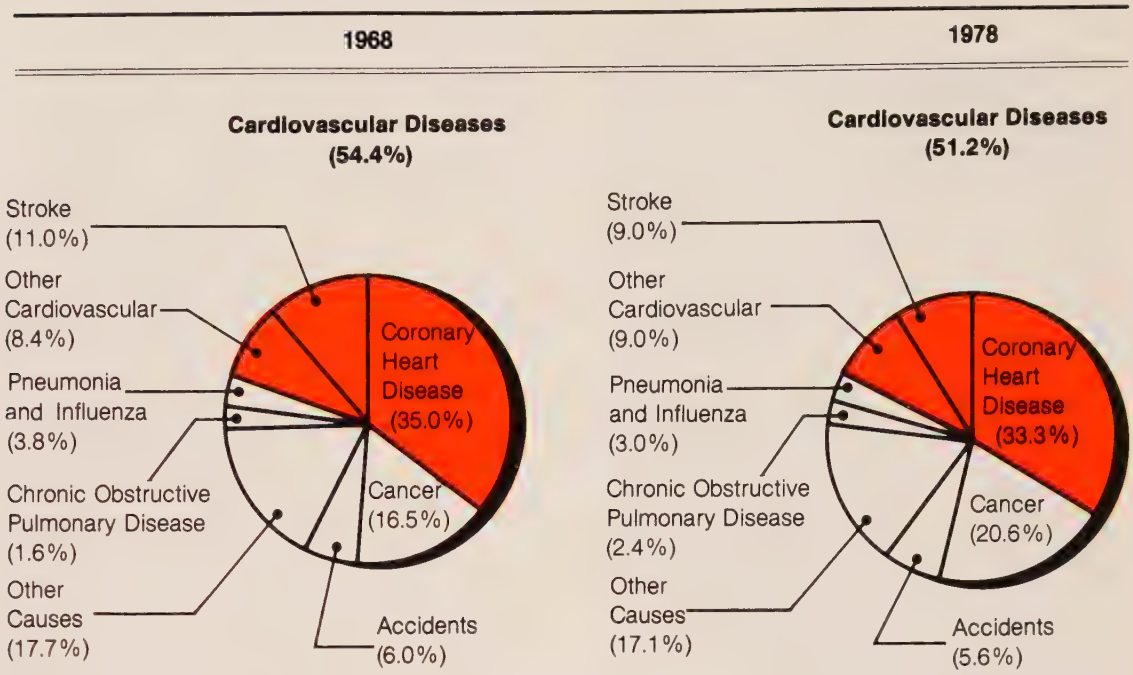
In economic terms, coronary heart disease costs the Nation more than any other disease—an estimated $27 billion each year, as measured in medical costs, lost wages, and lost productivity. It is responsible for:

- More than 650,000 deaths each year, almost twice as many as deaths from all forms of cancer, the second leading cause of death.
- About 150,000 deaths in the age group 35 to 64.
- As many as 1.25 million heart attacks each year, 20 to 25 percent of victims dying suddenly without receiving definitive medical care.
- The disability of 22 percent of the nearly 500,000 people receiving Social Security disability allowances.
- Some 18 million lost workdays due to illness, and 184 million days of restricted activity.
- Nineteen million hospital bed days, and 14.6 million physician office visits.
- Forty percent of the 4.8 million hospital discharges attributed to cardiovascular diseases in 1978.

Arteriosclerosis, the underlying cause of an estimated 86 percent of deaths from heart and vascular diseases, can evolve slowly, encroaching more and more on the inside diameter of the coronary artery for decades, without any signs or symptoms. Then, as a result of further vessel occlusion or vessel spasm, coronary heart disease will suddenly manifest itself as angina pectoris, heart attack, or sudden death. A disease so silent but so lethal has been difficult to diagnose, treat, and control.

Nevertheless, the precipitous decline of deaths due to coronary heart disease in recent years has clearly been real. The major cause is uncertain, but it is clear that both primary prevention—such as through reduced cigarette smoking, improved diet, blood pressure control, and exercise—and improved treatment have played a role. And, surprisingly, the decline in coronary heart disease can be seen in both U.S. majority and minority populations, in both males and females, and in every age decade from the third to beyond the eighth.

Figure 5.
Deaths by Cause and Percentage of Total Deaths, 1968 and 1978



Hypertension

Hypertension is the most commonly encountered form of heart and blood vessel disease. Affecting some 35 million Americans—23 percent of the adult U.S. population—it is defined by a blood pressure of 160/95 or higher, and is considered to exist in patients taking medication for the condition. An additional 25 million people have so-called borderline hypertension. These conditions are factors contributing to the deaths of at least 250,000 people in this country each year. The disease takes its toll by causing vascular complications that affect vital organs of the body, particularly the heart, brain, and kidneys. It is not only a major direct cause of cardiovascular disease, but also appears to greatly accelerate the atherosclerotic process, especially that of the coronary and cerebral vessels.

Table 2.
Number of Hospital Discharges and Days and Physician Office Visits for Patients with Cardiovascular Diseases, United States, 1978

First-Listed Diagnosis	No. Discharges (000)	Length of Stay in Days	No. Days (000)	No. Office Visits (000)
Total Cardiovascular	4,282	10.2	49,163	55,313
Rheumatic fever and rheumatic heart disease	114	10.8	1,235	1,000
Acute myocardial infarction	425	12.5	5,320	968
Other coronary heart disease	1,529	9.1	13,989	13,610
Hypertensive disease	317	6.8	2,168	24,968*
Cerebrovascular disease	648	13.4	8,700	2,270
Congenital heart disease	62	7.7	479	165
Other cardiovascular diseases	1,733	10.0	17,268	12,332

*An estimate of 51 million is given by the National Disease and Therapeutic Index, which includes visits in all locations (office, hospital, etc.) and by telephone.

SOURCE: Unpublished data from the Hospital Discharge Survey and the National Ambulatory Medical Care Survey, NCHS.

Table 3.
Economic Cost of Selected Diseases, 1975 (Dollars in Millions)

Diagnosis	Direct Costs		Indirect Costs				Combined Costs	
			Morbidity		Mortality			
	$	%	$	%	$	%	$	%
Diseases of the Circulatory System	15,999	16.1	8,735	15.1	25,674	29.2	50,408	20.0
Diseases of the Respiratory System	7,552	7.6	8,561	14.8	3,605	4.1	19,718	8.0
Diseases of the Blood and Blood-Forming Organs	696	0.7	289	0.5	264	0.3	1,249	1.0
Circulatory, Respiratory, and Blood Diseases Combined	24,247	24.4	17,585	30.4	29,543	33.6	71,375	29.0
All Diseases	99,374	100.0	57,846	100.0	87,926	100.0	244,146	100.0

SOURCE: Dorothy P. Rice *et al.* "The Current Burden of Illness in the United States," National Academy of Sciences, Washington, D.C., October 1976.

Most strokes, especially those that occur before age 65, result from hypertension, the *major* factor leading to more than 175,000 stroke deaths and 250,000 cases of stroke-inflicted disability each year. The World Health Organization estimates that stroke patients occupy more hospital and nursing home beds and make more use of social services than do cancer and accident victims combined. Moreover, hypertension is a *significant* factor in the 1.25 million heart attacks and 0.65 million heart attack deaths that occur each year.

The important epidemiological investigation known as the Framingham Heart Study demonstrated that coronary heart disease occurs three to five times more frequently in people with high blood pressure (160/95 or higher) than in people with normal blood pressure. A number of mechanisms can explain this relationship, and the relative importance of each is not established, but the recent decline in the death rate from coronary heart disease, at a time when the treatment of hypertension has improved, and recent clinical trial results reinforce that there is a cause and effect relationship.

Kidney failure associated with hypertension accounts for a significant number of deaths in the United States each year. In 1973, there were 35,000 deaths due to kidney failure; 12,000, or 30 percent, were associated with hypertensive disease.

In 1977, hypertension and its complications were estimated to cost the American public at least $8 billion in direct medical expenses and in income lost through illness, disability, premature loss of productivity, and death.

Although blood pressures above 160/95 are defined as hypertensive, cardiovascular risk begins to increase at considerably lower levels. For example, in a 35-year-old man with a normal blood pressure of 120/80, the risk of mortality over the next 20 years would increase almost twofold if his pressure were 142/90, and a level of 152/95 raises the 20-year mortality risk 2.5 times. With higher blood pressures, the mortality risk rises even more steeply.

In spite of a lack of knowledge about the mechanism of most forms of hypertension, preventative measures have been successful. Since 1972, the NHLBI-sponsored National High Blood Pressure Education Program has increased by more than 10 million the number of adult Americans aware of having hypertension, increased patient visits for hypertension by 50 percent, and increased by an estimated 6 to 10 million the number of Americans under effective blood pressure control. Moreover, the massive Hypertension Detection and Follow-up Program recently demonstrated the lifesaving value of antihypertensive therapy even in patients with borderline high blood pressure.

Chronic Obstructive Lung Disease

Respiratory diseases generally have a greater national impact as causes of ill health than as causes of death. Yet chronic obstructive lung

disease, which includes chronic bronchitis and emphysema, is the fifth leading cause of death and accounts for about 2.5 percent of all deaths. There were about 80,000 deaths from these and other chronic lung diseases in 1977.

Chronic obstructive lung disease, which afflicts more than 4 million people, in total accounted for about 45,000 deaths in 1977 and showed a 22 percent increase in the age-adjusted death rate from 1968. The increase was much greater in females than in males. The long-term upward trend for this group of diseases is further indicated by the eightfold increase in the age-adjusted death rate which occurred since 1950; in contrast, the death rate for all causes declined 27 percent during this period.

The rise in deaths from chronic obstructive lung disease is largely unexplained. There have been changes in nomenclature and death certification practices, and there has been considerable confusion resulting from variation among physicians in the use of different diagnostic labels for similar conditions. But it is thought that the increase in the combined rate is real; indeed, the appreciably greater increase in death rates for chronic obstructive lung disease in women than in men is consistent with changes in lung cancer death rates and smoking habits in women and suggests that at least some of the increase is real.

Another index of the importance of chronic obstructive lung disease is its cost to the Nation: $16.4 billion in direct and indirect costs. It is noteworthy that this figure ranks behind that of only four other causes: cardiovascular disease, accidents, digestive diseases, and cancer.

In 1977, chronic obstructive lung diseases accounted for more than 8.4 million visits to physicians and 321,000 hospital discharges. This group of diseases was responsible for 2.3 million hospital bed days, or an average stay of 7.1 days' length.

It is clear that a number of risk factors intervene in the development and aggravation of chronic obstructive lung disease, but present data indicate that smoking is by far the most important factor.

Viral Hepatitis

Viral hepatitis is the most common infection transmitted by blood and blood products and may be regarded as the most frequent transfusion complication. It remains a serious hazard for hundreds of thousands of blood recipients and results in prolonged incapacitating illness and often in chronic liver disease. According to recent prospective studies, the incidence of biochemically detectable posttransfusion hepatitis is between 7 and 10 cases for each 100 patients transfused, or 21 to 37 cases per 1,000 units of white or red blood cells transfused.

More than 3 million Americans receive transfusions annually; therefore, it is estimated that there are between 200,000 and 350,000 cases of posttransfusion hepatitis each year. Fortunately most of these cases are subclinical—that is, although laboratory evidence of liver damage can be found and many people become chronic carriers and transmitters of the virus, the illness is undetected and the patients do not require hospitalization or other acute medical care.

There are thought to be between 0.5 and 1.0 million chronic carriers of hepatitis viruses in this country. While highly sensitive tests to detect the hepatitis B virus have virtually eliminated hepatitis B as a transfusion hazard, it has now become apparent that another form of the disease, "non-A, non-B hepatitis," remains a major hazard. This form of liver infection, with clinical symptoms and an incubation time like those of hepatitis B, is now responsible for 90 percent of transfusion-transmitted hepatitis cases in the United States.

Legislative Mandate: Strengthening National Response

The gaps in our knowledge and management of heart, lung, and blood disorders continue to pose a bold challenge to the medical and scientific communities. Recognizing its responsibility to act decisively on behalf of the health and vitality of the Nation, Congress passed the National Heart Act of 1948 (P.L. 80-665), which established the National Heart Institute by adding a new section to the Public Health Service Act. In the years since, Congress has reendorsed the Institute's authorization and expanded its mandate four times. These revisions have greatly increased not only the enormity of NHLBI's responsibilities, but also the potential for improving the Nation's health. The following chart indicates the evolution of the responsibilities that have resulted from particular legislative actions.

1972 Legislation

Through the National Heart, Blood Vessel, Lung, and Blood Act of 1972, Congress strengthened its commitment to the Institute and to research in its disease areas. The name change from National Heart Institute to *National Heart and Lung Institute* was codified to statute and the Institute was given expanded responsibilities which added several new sections to the Public Health Service Act.

To carry out these broadened responsibilities most effectively, the Institute needed a new program strategy. Thus, the law mandated that the Director of the Institute, with the advice of the Council, develop a *national plan* within 180 days of the law's enactment. A thorough review was undertaken of the state of scientific research in heart, lung, and blood diseases, including input from hundreds of experts in these fields. The resultant plan outlined a comprehensive *National Heart, Blood Vessel, Lung, and Blood Diseases Program* based on responsibilities outlined in the law for:

- research into the *epidemiology, etiology, and prevention* of heart, blood vessel, lung, and blood diseases;
- research into *basic cardiovascular biological processes;*
- development and evaluation of *techniques, drugs, and devices* to aid diagnosis and treatment;
- programs to develop *technological devices* to assist, replace, or monitor vital organs;
- *field studies and large-scale tests* relating to those diseases;
- research into *blood diseases and the use of blood resources* in the United States, including such items as collection, preservation, fractionation, and distribution;
- *education and training* of scientists and clinicians;
- *public and professional education* programs in all aspects of those diseases;
- programs to research and study heart, lung, blood vessel and blood *diseases of children;* and
- programs to research and develop *emergency medical services,* including training of paraprofessionals and development of specialized equipment and communications.

The National Program has continued to be the foundation of the Institute's activities, and is updated each year. As a provision of the 1972 legislation, Congress mandated that the *Director of the Institute* submit an *annual report* to the President, for transmittal to Congress, on the accomplishments of the National Program during the preceding year and plans for the next 5 years.

The Act also mandated an *annual report from the Advisory Council* to the President, for transmittal to Congress. Membership on the Council was expanded from 16 to 23 members, including for the first time representatives from the public and from medical residency training programs. Corresponding to the Institute's increased mandates, the Council's functions expanded from concern with heart diseases to concern with heart, blood vessel, lung, and blood diseases.

To complete its expansion of Institute mandates, the 1972 Act:

- established a specific post of *Assistant Director for Health Information,* to provide the public and health professionals with information about cardiovascular and pulmonary diseases, including emphasis on the effects of lifestyle factors such as diet, smoking, exercise, and stress;
- required the Institute to establish *prevention and control programs* with other governmental and private health agencies with appropriate emphasis on children's diseases, and delineated authorization of appropriations for that purpose;

- authorized the establishment of up to 30 *national research and demonstration centers* (15 for heart, blood vessel, and blood diseases, and 15 for lung diseases, including lung diseases of children), to foster coordinated programs in basic and clinical research, training, and demonstration;
- established an *Interagency Technical Committee,* chaired by the Director of the Institute, to coordinate those aspects of all Federal health programs related to heart, blood vessel, lung, and blood diseases and blood resources; and
- specified that a minimum of *15 percent* of appropriated funds must be utilized for programs in lung diseases, and a minimum of *15 percent* for programs in blood diseases and blood resources.

From 1948 until 1972, the Institute received appropriated funds under the general research authority of Public Health Service Act Section 301, which have no specific disease category allocation or "time and dollar" limits. Beginning with the 1972 legislation, Congress designated a specific authorization level and renewal period for the Institute. (Similar action had taken place regarding the National Cancer Institute, in 1971.) The 1972 Act authorized 3 years of funding; thus, the Institute required reauthorization after June 30, 1975.

1975-1976 Legislation

Reauthorization legislation for the National Heart and Lung Institute proceeded through Congress during 1975, was delayed into 1976, and was signed in April 1976. It provided for a 2-year renewal period, rather than 3 years, so that the next reauthorization would coincide with that of the National Cancer Institute and with publication of the President's Biomedical Research Panel Report. Thus, reauthorization in the Health Research and Health Services Amendments of 1976 provided funding authority for fiscal years 1976 and 1977. (Note: During this period, the fiscal year start was shifted from July 1 to October 1 through an act of Congress.)

The significant thrust of the 1975-1976 legislation was to emphasize, clarify, and expand the Institute's role in blood-related areas. This intention took form in several actions, including the following:

- Congress changed the Institute's name to the *National Heart, Lung, and Blood Institute* and changed the Council's name to the *National Heart, Lung, and Blood Advisory Council.*
- In the several Public Health Service Act sections where Institute responsibilities regarded "heart, blood vessel, lung, and blood diseases," Congress added language about *"the use of blood and blood products and the management of blood resources."*
- Blood diseases and blood resources were added to cardiovascular and pulmonary diseases, as areas of *information dissemination* mandated for the Institute's Office of Prevention, Education, and Control.
- The distribution of up to 30 national research and demonstration centers was reorganized into *10 centers for heart, 10 centers for lung, and 10 centers for blood.*
- Committee report language emphasized that Congress intended the Institute to function as the *locus of coordination* for blood research programs and research in the management of blood resources.

Other notable highlights of the 1975-1976 legislation included:

- a new authority for the Advisory Council, to recommend to the Secretary areas of research to be supported by *contracts*, and recommended the percentage of the Institute's budget to be expended for contracts;

- changes in the annual *Director's Report*, to be submitted after the end of each fiscal year rather than calendar year, and to include personnel and appropriations estimates for the following 5 years; and
- changes in the annual *Advisory Council Report*, to be transmitted simultaneously to the President and Congress rather than to the President for transmittal to Congress, and to be transmitted by November 30 each year rather than by January 31.

1977 Legislation

Because both Congress and a new Administration were interested in undertaking a major review of all biomedical research authorities through extensive "biomedical overview" hearings and reports, the Biomedical Research Extension Act of 1977 was a 1-year renewal.

Congressional hearings began a series of discussions on several substantive issues in the conduct and management of biomedical research, while the legislation was kept to as simple an extension as possible. In the 1977 legislation, Congress:

- *reaffirmed the need for an expanded, intensified, and coordinated National Program,* as mandated in the previous NHLBI authorization laws; and
- included a few *technical amendments* clarifying the role of research and demonstration centers for blood, adding cost-of-living increases for the centers in general, and reassigning one ex-officio Council membership space from the National Science Foundation back to the newly reestablished Office of Science and Technology Policy.

1978 Legislation

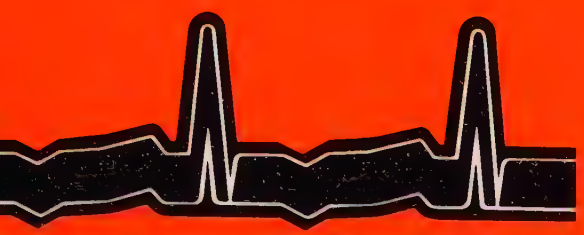
The Biomedical Research and Research Training Amendments of 1978 resulted from a compromise between two sets of concerns. From the perspective of "biomedical overview," several major issues were still being explored, and future hearings were being planned; thus, another 1-year simple extension renewal was a possibility. From the perspective of research funding stability and planning needs, however, a 3-year renewal period was also proposed. The final law reauthorized the Institute for 2 years, FY 1979 and FY 1980, and included several amendments to further increase the effectiveness of the Institute's programs.

The most significant amendments affected the submission of reports and responsibilities for information dissemination.

- Transmittal requirements for the *Director's Report* were changed to correspond to the Council Report route and timing, so that the Secretary transmits both reports, by November 30 of each year, simultaneously to the President and Congress.
- Language was added to the existing information dissemination mandates, requiring that dissemination occur *"on a timely basis."*
- In the dissemination program of the Office of Prevention, Education, and Control, responsibilities were added for *"nutrition"* (in addition to "diet") and *"environmental pollutants."*
- Research and demonstration centers were required to have programs of *continuing education* for health and allied health professionals, and *information programs* for the public.

Additional technical amendments included a reimbursement provision for *experts and consultants.*

Authorizations of appropriations will expire on September 30, 1982. During the winter and spring of 1982, Congressional committees will consider reauthorization bills to continue the activities and programs of the National Heart, Lung, and Blood Institute.



2

National Program Plan:

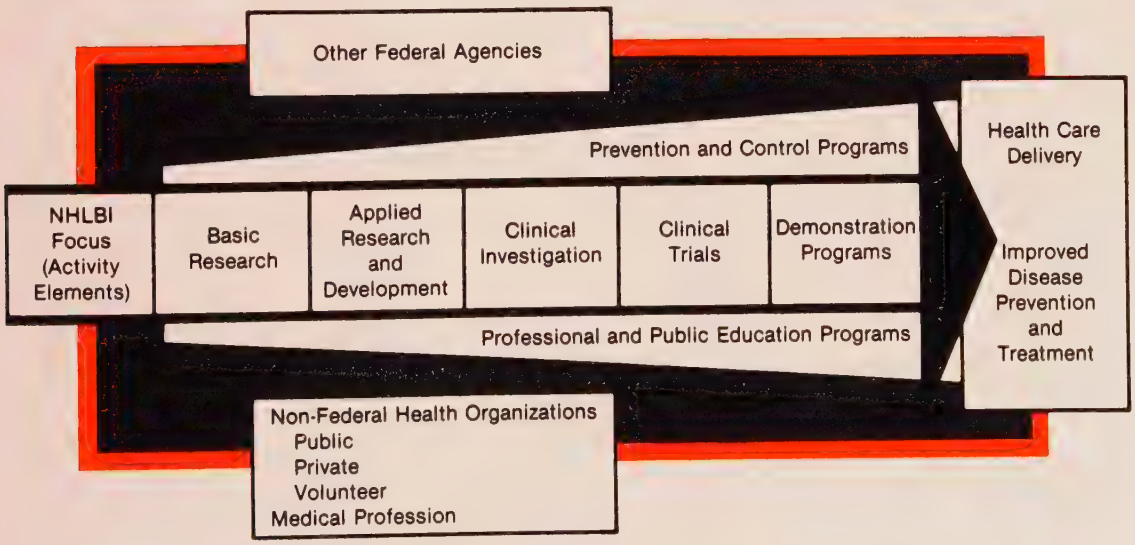
Advancing Biomedical Research

To direct society's approach toward combating heart, lung, and blood diseases, NHLBI has developed the comprehensive National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program, guided by a Five-Year National Program Plan. In its annual update of this plan, the Institute makes use of information and advice from the public, the medical community, technical sources, and other Federal and non-Federal agencies and organizations. The scientific community prominently participates in reviewing program goals, assessing progress, and recommending directions for the future. The Institute uses this information exchange to weigh accomplishments, assess opportunities, and strengthen its programs.

While the National Program Plan addresses specific scientific goals and individual program areas, there is an overriding strategy that gives direction and momentum to the National Program as a whole. This unifying strategy is represented by the biomedical research and clinical applications spectrum illustrated in figure 6. All of the National Program's endeavors are directed toward systematically advancing progress through this spectrum.

The National Program itself includes basic, applied, and clinical research, clinical trials, demonstrations, and public and professional education activities. NHLBI cooperates with many other Federal organizations to translate these activities as expeditiously and effectively as possible to practical health care. All program activities are directed by an overall strategy which aims to identify, develop, and promote prompt adoption of prevention and treatment approaches that are scientifically valid, socially and ethically acceptable, and economically feasible. The approach represents an ordered sequence consisting of the acquisition of new knowledge, testing and evaluation of promising hypotheses, and dissemination and application of this new and existing knowledge. The Institute's strategy is intended to maximize the beneficial effects of research findings on clinical practice and on the health-related behavior of the American public.

Figure 6.
The Biomedical Research Spectrum



The following paragraphs outline the steps in the NHLBI National Program strategy represented in the biomedical research spectrum.

Basic research on disease etiology and pathogenesis is the keystone of the biomedical research spectrum. This stage of research seeks fundamental knowledge at the level of molecules, cells, tissues, organs, and population groups. NHLBI devotes a major share of its resources to furthering scientific understanding of fundamental life processes as they relate both to the normal functions of the heart, lungs, and blood and to their disorders.

Another step in the biomedical research spectrum, *applied research,* is focused on specific knowledge concerning means of prevention, diagnosis, or treatment of a specific disease or disorder. Like basic research, applied research seeks to develop knowledge and proceeds one step further to apply this knowledge systematically to the solution of identified health problems.

Clinical research is the vital link between basic and applied research and clinical practice. It provides the mechanisms for translating fundamental research results into potential clinical regimens. Clinical investigations, coupled with basic and applied research, are critical for the development of effective therapies to alleviate or delay the effects and progression of disease and promote new and more effective preventive measures.

Clinical trials are the scientific means to validate potential health care treatments and techniques. Such trials carefully test the effectiveness and safety of therapeutic approaches. Validation is critical to determining whether a given preventive measure, diagnostic technique, or therapy is ready for widespread use, whether it requires further refinement, whether it should be used only under special circumstances, or whether the approach is not workable and should be discouraged.

Demonstration programs as well as *prevention, education, and control programs* carry biomedical research into the realm of medical practice. Demonstration programs explore ways of introducing health care advances into clinical practice. Prevention, education, and control programs provide the means to encourage widespread acceptance and implementation of validated health care practices.

All of the Institute's scientific endeavors are directed at systematically advancing progress through the biomedical research spectrum— with the ultimate goal of improved health care. In marshalling its resources toward this end, the Institute has organized 3 categorical Divisions concerned with the 20 disease-specific program areas represented in the National Program Plan. (See figure 7 and table 4.)

Each of the three categorical Divisions has certain responsibilities and objectives in common

Figure 7.
NHLBI Organizational Structure

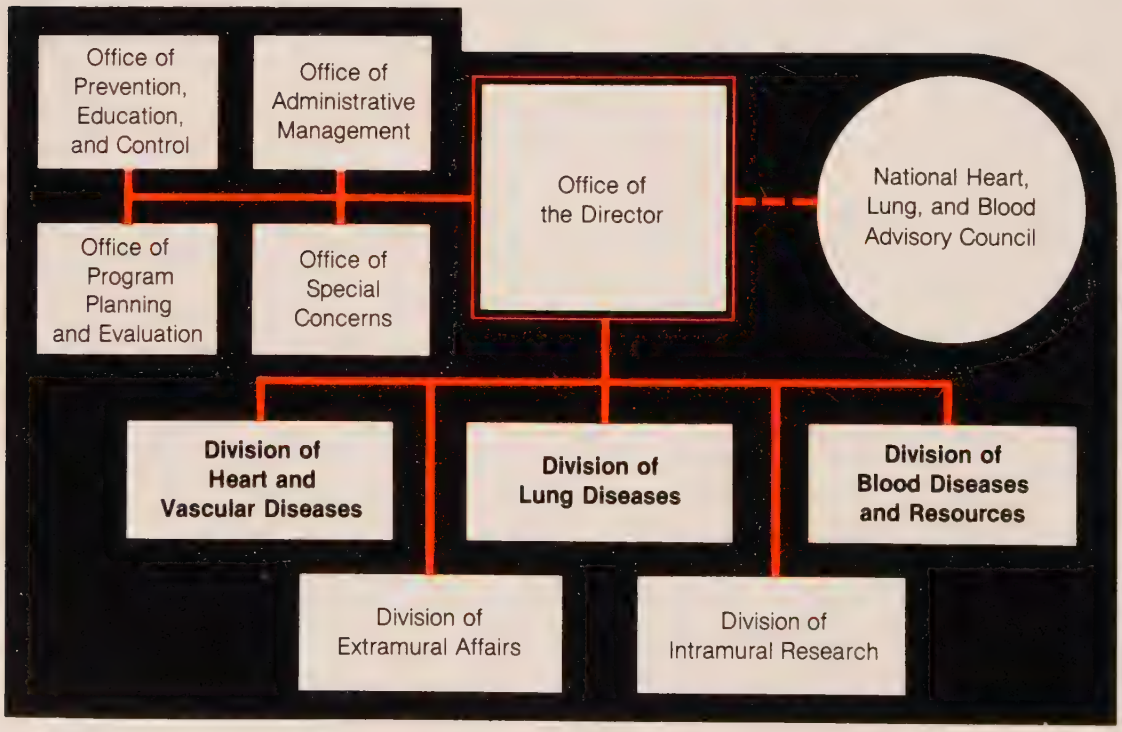

Office of Prevention, Education, and Control
Office of Administrative Management
Office of the Director
National Heart, Lung, and Blood Advisory Council
Office of Program Planning and Evaluation
Office of Special Concerns
Division of Heart and Vascular Diseases
Division of Lung Diseases
Division of Blood Diseases and Resources
Division of Extramural Affairs
Division of Intramural Research

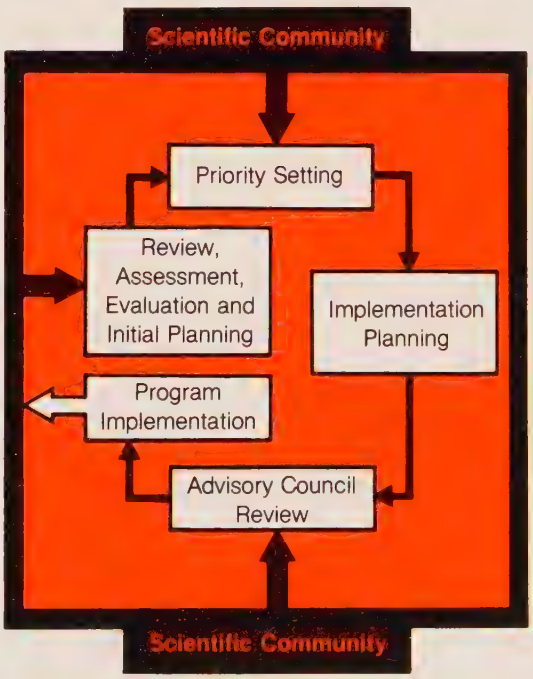
Table 4.
National Program Elements by Division

	Division of Heart and Vascular Diseases	Division of Lung Diseases	Division of Blood Diseases and Resources
Program Elements	Arteriosclerosis Hypertension Cerebrovascular Disease Coronary Heart Disease Peripheral Vascular Disease Arrhythmias Heart Failure and Shock Congenital and Rheumatic Heart Diseases Cardiomyopathies and Infections of the Heart Circulatory Assistance	Structure and Function of the Lung Chronic Obstructive Lung Diseases Pediatric Pulmonary Disease Fibrotic and Immunologic Interstitial Lung Diseases Respiratory Failure Pulmonary Vascular Diseases	Bleeding and Clotting Disorders Red Blood Cell Disorders Sickle Cell Disease Blood Resources

with the others: increasing knowledge of normal and diseased organ systems through broad programs of basic and clinical research, clinical evaluation of research findings, and expediting the transfer of validated findings into medical practice; emphasizing programs of prevention; planning and coordinating research grant, contract, and training programs; evaluating existing activities and assessing future needs; and stimulating the health care communities to respond to identified needs. In addition, each Division promotes activities specific to its own mission. For example:

- Division of Heart and Vascular Diseases—application of research findings to the prevention and cure of cardiovascular disorders and diseases such as arteriosclerosis, high blood pressure, and coronary heart disease.
- Division of Lung Diseases—expansion of the knowledge base for diseases such as emphysema, chronic bronchitis, and pulmonary diseases of children to solve immediate national problems.
- Division of Blood Diseases and Resources—emphasizing bleeding and clotting disorders, sickle cell disease, Cooley's anemia, and other

Figure 8.
Steps in the NHLBI Planning Process



diseases of the red blood cell; seeking means to the optimal development and management of the Nation's blood resource.

NHLBI uses an integrated, continuous process to plan, implement, and evaluate the National Program. This process, illustrated in figure 8, was established to respond to legislative mandates, to identify and pursue the most promising opportunities, and to make effective use of resources. The planning cycle is designed to ensure a thorough review of the entire National Program as well as the implementation of new programs and the expansion, modification, or discontinuation of existing programs. Throughout the cycle, information is drawn from the scientific and medical communities, the public, and other Federal and non-Federal organizations. Participation of the scientific community is crucial because of the inherent difficulty in assessing the relative values of research accomplishments and alternatives for future program activities.

Review, assessment, evaluation, and planning of programs is done through a review of goals, objectives, and progress of the Five-Year National Program Plan with respect to the state of the science and the impact of the program on medical care and the health of the public. This is accomplished with the participation of the NHLBI program staff, scientific advisory committees, and members of the general scientific community, through workshops, task forces, and technical working groups convened to reach consensus on future directions. The results of evaluation studies are also applied. This step produces an update of the Five-Year National Program Plan and a preliminary list of program initiatives and recommended program directions for future years, together with revised objectives where appropriate.

Priority setting is the second step in the process, in which proposed new initiatives for implementation in the next year are ranked jointly by the staff of the Institute's categorical Divisions and appropriate advisory committees.

Implementation planning constitutes the third step, in which the staff of the categorical Divisions and the Office of the Director convert the ranked initiatives into specific program plans including programmatic justification, management and fiscal plans, and funding mechanisms.

Advisory Council review consists of a thorough examination of the implementation plan by the full National Heart, Lung, and Blood Advisory Council. Council advice and recommendations are solicited for development of the final NHLBI Implementation Plan and Program Budget.

Program implementation consists of translating specific mandates and approved initiatives contained in the implementation plan into operational projects through various types of grants and contracts, intramural research, collaboration with other Federal agencies through interagency agreements, and jointly supported international activities.

In the past year, several working groups and task forces have assessed the Institute's scientific and educational progress. The processes employed by these groups and their recommendations are excellent examples of NHLBI planning and assessment activities.

NHLBI designated the *Working Group on Heart Disease Epidemiology* to develop a report indicating key areas of epidemiological research needed to deepen understanding of cardiovascular disease. The group was concerned with population trends in cardiovascular disease, with precursors and causes, and with optimal efforts to control these diseases and their causes. In particular, the working group made research recommendations in the following areas:

- **Community surveillance**—To monitor trends of incidence of fatal and nonfatal coronary heart disease and its relation to changing risk factors, NHLBI should initiate prospective surveillance of the populations of 10 communities across the country.
- **Longitudinal studies**—Careful longitudinal studies, some starting at birth, others in adolescence, should be developed to determine the interplay between environmental and genetic variables leading to an increase in heart disease risk factors prior to middle age.
- **Salt**—Clinical trials of the effects of reduced salt intake are needed in infants, children, and adults to assess the role of salt in blood pressure regulation.
- **Physical activity**—Methods should be developed for the more precise measurement and description of physical activity and fitness in the general American population and in specific subgroups.
- **Risk factor variability**—Studies should be pursued to determine the dynamic short-term changes in risk factors and behavior (blood pressure, serum cholesterol, weight, activity, and smoking) that occur during the challenges of daily life and the role of variability of risk factors as predictors and determinants of disease.
- **Occupational exposures**—Studies among occupational groups to determine the role of chemical and physical exposures in the etiology of hypertension, coronary heart disease, and sudden death are needed both on a nationwide basis and in specific localized industries with specific exposures hypothesized to be high risk.
- **Type A behavior pattern**—Continued research of this behavior pattern (a combination of psychosocial variables centered on time-pressure)

is needed, with special emphasis on further prospective assessment of its role as a risk factor, its predictive power in various population groups, its determinants, and the biological mechanisms possibly linking a type A behavior pattern to coronary atherosclerosis and its manifestations.

- **Social change and mobility**—Further study of persons experiencing social change, migration, and mobility is needed, with particular emphasis on geographic and cultural groups known to exhibit different rates of coronary heart disease.
- **Cigarette smoking**—Major research efforts on the health aspects of smoking should continue, with the goal—through effective mass public education—of progressively reducing and eliminating this habit among Americans. Surveillance of smoking behavior nationally, regionally, and in major socioeconomic and ethnic strata should be continued and expanded to include objective measurements of smoking and dose.
- **Evaluation of intervention techniques**—NHLBI should sponsor studies to extend common epidemiological methods of evaluating the quality of cardiovascular medical care and the after-the-fact consequences of new treatments and interventions.
- **Water hardness**—The differences in coronary heart disease mortality rates reported in several studies between geographic areas differing in hardness of local water supplies need to be validated and explained.
- **Training**—NHLBI should expand educational programs in cooperation with epidemiology departments in schools of public health and with departments of preventive medicine that have substantial strength in cardiovascular epidemiology.

Specific recommendations have been made in each of these areas and the Institute is considering them within its overall goals and objectives reviews.

A similar Institute undertaking has been creation of the *Task Force on Epidemiology of Respiratory Diseases*. NHLBI has long recognized the importance of epidemiologic studies, but for several reasons this facet of the lung program has been slow to develop. Some obstacles—the cost and long-term commitment required—are inherent in the epidemiological approach. These difficulties have been coupled with the absence of a well-defined plan for a lung program based on an in-depth analysis of the state of knowledge and unmet needs in this area of investigation. Since May 1978, when the 13-member task force was formed, more than 60 epidemiologists, biomedical researchers, and pulmonary physicians have been addressing this problem. Recommendations contained in the final report will provide an impetus to the Division's epidemiology program, similar to the stimulus the reports of the Task Force on Research in Respiratory Diseases, and of the Task Force on Prevention, Control, and Education in Respiratory Diseases, have given other facets of the lung program.

The *Hypertension Task Force* was charged by the NHLBI to assess the current state of hypertension research. The report of this influential group was published during the past year and is summarized in Chapter 6, Special Emphasis Areas for 1980.

NHLBI conducted the *Workshop on the Thrombotic Process in Atherogenesis* to bring together experts in hemostatic phenomena and in atherogenesis to discuss the current state of knowledge in thrombosis and atherogenesis. The workshop participants developed recommendations for future research that will serve both individual investigators and agencies that support research. The key areas designated for future research were:

- Studies to determine the relative contribution of thrombosis to plaque growth;
- Studies to determine at what stage in the life of the individual and of the plaque, thrombosis may occur;
- Studies to identify possible subsets of populations in which thrombosis is a dominant factor;
- Detailed studies of the relationship among dietary and plasma lipids and thrombosis.

The *Workshop on Physical Conditioning and Cardiovascular Rehabilitation* was convened to discuss the development and application of methods to evaluate cardiovascular and other responses to exercise as a technique of rehabilitation in patients who have manifestations of heart disease. Workshop participants recommended:

- Concentration of efforts in small, pilot, randomized studies of specific subgroups of cardiovascular patients. These studies would seek to clarify the value of training and other alterations of multiple risk factors in new programs of cardiac rehabilitation.
- Pursuit of behavioral studies and testing programs involving the psychological and social aspects of rehabilitation.

The *Workshop on Percutaneous Transluminal Coronary Angioplasty* (a method for widening a narrowed coronary artery by threading a balloon catheter through the blood vessel, inflating and quickly deflating the balloon to compress an obstruction of atherosclerotic plaque, and then removing the catheter) brought together investigators who had submitted research protocols as

well as baseline outcome data on patients treated with PTCA. The participants presented their comments on the development and evaluation of this technique and gave advice about future studies. The group recommended:

- Additional basic and clinical research;
- Development of a registry to monitor the level of experience and reporting on possible adverse effects and potential benefits of the technique;
- Deferment of a randomized clinical trial because of the rapidly changing technology, the need for better definitions of indicators for the technique, and the limited number of appropriate patients for study.

At the NHLBI-sponsored *Workshop on Noninvasive Techniques for Assessment of Atherosclerosis in Peripheral, Carotid, and Coronary Arteries,* investigators reviewed the state of the art of noninvasive diagnostic methods as alternatives to conventional angiography. Currently the acceptable clinical method for measuring atherosclerotic lesions, angiography, is timeconsuming, expensive, and variable in its sensitivity and specificity, and carries a small but significant risk to the patient. Presentations and discussions by workshop participants focused on the potentials and limitations of a number of techniques for noninvasively imaging and assessing atherosclerosis: ultrasound, X-rays, nuclear magnetic resonance, gamma and positron emission tomography, and microwaves. The chemical and structural characteristics of the atheromatous plaque were also discussed.

The group agreed that the two noninvasive techniques currently providing the most reliable information and which have the greatest application are ultrasound and enhanced X-ray techniques.

Ultrasound B-scan modes combined with Doppler flow systems now are capable of visualizing atherosclerotic lesions in carotid arteries and imaging shallow peripheral arteries. Several studies indicate that this method can detect smaller lesions with greater precision than angiography. The B-scan mode offers a distinct advantage over angiographic views because of its ability to obtain both transverse and longitudinal images of blood vessels, their internal shape and diameter (their lumen), and any lesions. The Doppler flow data provide information about abnormalities of blood flow which may indirectly indicate plaque surface characteristics.

Computerized X-ray methods in conjunction with intravenously injected contrast agents and two views are feasible for imaging the lumen of carotid and peripheral arteries. This technique has the potential for providing the same information as angiography with significantly less risk, because studies indicate that this method has the potential for visualizing the lumen of the coronary arteries with a resolution on the order of fractions of a millimeter.

Both ultrasonic and intravenous X-ray techniques, as well as the other noninvasive methods discussed, are in a state of rapid technological development. This progress promises to lead to improved resolution, range, and versatility. The group stressed that, as these techniques advance beyond research into the clinical area, validation with regard to clinical usefulness must be considered. Validation must not be limited to testing the accuracy of measurements but must also include testing the reproducibility of image generation and interpretation. Carefully controlled studies must include pathologic data from surgical and autopsy specimens in animals and humans. The increasing clinical use of ultrasound imaging, in particular, makes validation of this technique most pressing.

These are but a few examples of the special task forces, working groups, and workshops NHLBI has established during the past year to assist it in assessing its progress, examining the state of knowledge, identifying opportunities, and planning for future research. Such groups provide invaluable information to the NHLBI planning process. Often they point out major gaps in current knowledge or research sponsorship. Frequently they provide insight concerning newly conceptualized interrelationships among disease entities, findings of basic research, previously less integrated disciplines, or new techniques of investigation. Besides considering technical matters, such groups often can give a more balanced perspective of the relative value and priority of areas of study or clinical needs. They direct the Institute's attention to new ways to approach persistent problems and frequently assist in identifying the most practical and economical approaches. In addition to conferring scientific authority in the planning effort, these activities assess the availability of expert personnel resources, the availability of study populations, the state of technologies for use in investigations, and the appropriateness of particular studies at a given point in time. It is through the overall planning process and the contribution of information resources such as these that NHLBI is able to direct a balanced, feasible, and efficient program of research.

3

Program Goals and Planned Activities:

Charting the Course for 1982–1986

The possible avenues of research in heart, lung, and blood diseases are limited only by the imagination of the thousands of investigators working in disciplines related to the NHLBI mission. To direct the fertility of scientific minds into a logical framework of inquiry, the scientific staff of the Institute, with extensive input from NHLBI advisory committees and task forces, develops program goals and planned research activities. Other leading research experts are called upon to contribute their specialized knowledge in reviewing proposed goals and activities. After agreement is reached, the program goals and activity plans are presented to the National Heart, Lung, and Blood Advisory Council for its considerations.

The general program goals for 1982 through 1986 indicate areas of research priority. The activity listings indicate major areas of emphasis but are not all-inclusive. New areas are continually being evaluated, as the Institute seeks to maintain the flexibility to fund research in new areas that show promise. Throughout this process, NHLBI gauges investigative pursuits according to their potential for advancing the state of science; for making effective use of available manpower, facilities, and funding; indeed, for producing results "important to mankind."

Heart and Blood Vessel Diseases

For more than 50 years, heart and blood vessel diseases have been the major cause of death in the United States. Despite a continuing decline in cardiovascular mortality, each year over half of all deaths are caused by cardiovascular disorders, and more than two-thirds of all deaths of people over 65 years of age are attributable to heart and blood vessel diseases.

The National Program concerns itself with 10 major research areas related to heart and blood vessel disorders: arteriosclerosis, hypertension, cerebrovascular diseases, coronary heart disease, peripheral vascular diseases, arrhythmias, heart failure and shock, congenital and rheumatic heart diseases, cardiomyopathies and infections of the heart, and circulatory assistance. The National Program also stresses a major effort in prevention, control, and education. This effort focuses on demonstrations, communications programs, and training in areas of high impact where the state of the art is sufficiently advanced to allow meaningful clinical applications of research findings. The areas of emphasis in prevention, control, and education are hypertension (or high blood pressure), arteriosclerosis, coronary heart disease, congenital heart disease, and rheumatic fever.

Extramural and intramural research programs in heart and blood vessel diseases support investigator-initiated basic, applied, and clinical projects in all 10 Program areas. Contract research is being carried out in promising areas of research and demonstration that the Program desires to stimulate.

Arteriosclerosis

Program Goals

The Institute's mission is to improve the diagnosis, treatment, cure, and prevention of arteriosclerosis and arteriosclerotic disease beyond that which is possible at present. The following goals have been developed to serve as guidelines for research activities during the next 5 years:

- Gain a better understanding of the pathogenesis of arteriosclerosis.
- Further specify the causes, correlates, and associated risk factors for arteriosclerosis.
- Define those circumstances that may promote the regression of arteriosclerosis.
- Develop preventive measures against arteriosclerosis.
- Improve the diagnosis of arteriosclerosis and its risk factors.

Planned Activities

Fundamental research on the etiology and pathogenesis of arteriosclerosis; the biology of blood

vessels; regression and development of arteriosclerotic lesions; new risk factors; research in basic, clinical, and population aspects of arteriosclerosis, continuation of the Multiple Risk Factor Intervention Trial and the Lipid Research Clinics Coronary Primary Prevention Trial; and development and testing of noninvasive methods of detection and monitoring of arteriosclerosis.

Hypertension

Program Goals

A better understanding of the physiological systems that control blood pressure, and of the means by which these systems can initiate and/or exacerbate the development of hypertension, which could result in a significant reduction in the incidence of the condition. More effective therapy for those already afflicted is another potential benefit. The following basic goals have been established by the Institute as guidelines for research during the next 5 years:

- Emphasize research on etiology and pathogenesis of hypertension.
- Encourage development of improved methods and techniques for all aspects of hypertension research.
- Broaden the interdisciplinary base for contributions to hypertension research by attracting scientists to this field who traditionally have not been involved, or those unaware of the magnitude of their potential contributions if their efforts were directed toward this area of research.
- Evaluate the basic and clinical research implications of the Hypertension Detection and Follow-up Program (HDFP) and implement appropriate actions to improve patient care.
- Implement effective models of high blood pressure control on a community-wide basis.

Planned Activities

Fundamental research on inhibitors of kinins, kallikreins, and prostaglandins to understand more fully the physiological actions of these hormones; basic and clinical activities focused on the role of salt and weight control, fundamental investigations toward improved diagnosis, treatment, and prevention of hypertension; and a broadly focused hypertension education program directed toward the general and medical public.

Cerebrovascular Disease

Program Goals

The mission of the NHLBI in the area of cerebrovascular disease is to elucidate the etiology and pathogenesis of the vascular components of cerebrovascular disease and to enhance programs that will accomplish this goal. Thus, the major goals of the program are to:

- Gain further basic understanding of the pathogenesis of cerebrovascular disease.
- Encourage increased research activity exploiting the recent development of animal models of cerebrovascular disease.
- Develop noninvasive instrumentation to facilitate diagnosis and observation of disorders of the large vessels supplying the brain.

Planned Activities

Intensive study of the etiology and pathogenesis of cerebrovascular disease; and development of animal models.

Coronary Heart Disease

Program Goals

The ultimate objective directing the Institute's choice of program goals for the next 5 years is to decrease even further the mortality from coronary heart disease. The essential thrust of already established programs will be continued together with ongoing assessment procedures. The specific goals through which the Institute plans to enhance the reduction in death and disability from coronary heart disease are the following:

- Improve the recognition and assessment of latent coronary artery disease and overt coronary heart disease.
- Monitor trends of incidence of fatal and nonfatal coronary heart disease in relation to changing risk factors.
- Improve the therapy of patients with acute myocardial infarction and patients with chronic ischemic heart disease.
- Assess the proper role of coronary bypass surgery in the management of ischemic heart disease.
- Assess possible methods for the reduction of the incidence of sudden cardiac death.
- Develop techniques for reducing the amount of heart muscle irreversibly damaged during the course of myocardial infarction.
- Develop methods of reducing the incidence of recurrent myocardial infarction.
- Improve rehabilitation of patients with coronary heart disease.
- Assess the proper role of percutaneous transluminal coronary angioplasty in the management of ischemic heart disease.

Planned Activities

Studies to limit the myocardial damage to coronary events; development and testing of new techniques of emergency cardiovascular diagnosis and therapy; investigation of the mechanisms and factors which precipitate acute coronary events; and major clinical trials including the Beta-Blocker

Heart Attack Trial (BHAT), Multicenter Investigation of Limitation of Infarct Size (MILIS), and Coronary Artery Surgery Study (CASS), a coordinated attack to improve the management of coronary heart disease.

Peripheral Vascular Diseases

Program Goals

The Institute's broad goal in the area of peripheral vascular diseases for the next 5 years is to improve techniques for the diagnosis and treatment of peripheral arterial and venous diseases. Specific goals over the next 5-year period are to:

- Develop more effective noninvasive methods of evaluating the severity of peripheral arterial disease, suitable for the assessment of symptomatic patients, for the recognition of latent arterial disease, and for research assessment of new modes of therapy designed to retard or reverse atherogenesis.
- Improve management of patients with peripheral arterial disease, with particular attention to the long-term effects of arterial grafts and the improvement of graft techniques for smaller arterial vessels.
- Encourage greater research effort on the causes and treatment of peripheral venous diseases.

Planned Activities

Studies to improve the diagnosis, therapy, and rehabilitation of peripheral arterial, venous, and lymphatic diseases; studies of the natural history of occlusive venous disease with and without surgery; studies of the effectiveness of various therapeutic procedures and drugs; and noninvasive techniques for diagnosis and monitoring.

Arrhythmias

Program Goals

Now that sophisticated monitoring systems routinely provide data on the variety and characteristics of arrhythmias, the focus of NHLBI research is on improving the understanding of lethal arrhythmias and the means to prevent them. Consequently, the broad goals of the Institute now are to define the fundamental processes of electrical rhythm and conduction disorders and to develop methods of acute and chronic preventive therapy. Specific goals of the Institute over the next 5 years are the following:

- Develop improved understanding of the mechanisms whereby arrhythmias arise.
- Develop methods of chronic prophylactic therapy, using pharmacological agents, to prevent sudden cardiac death.
- Assess the role of pacemakers in the management of various conduction disturbances and define the indications for their use.
- Achieve a better understanding of the significance of rhythm disturbances commonly found in long-term, ambulatory monitoring of electrocardiographic rhythm to permit clinical management.
- Develop more effective methods for the recognition of those at heightened risk of sudden cardiac death.

Planned Activities

Investigation directed at fundamental understanding and prevention of arrhythmias; and studies of sudden death and improvement of methods to prevent, diagnose, and manage arrhythmias and other electrical disturbances of the heart.

Heart Failure and Shock

Program Goals

In the next 5 years the Institute plans to define mechanisms more fully, improve diagnostic techniques, and develop methods for the prevention and treatment of heart failure and shock of cardiogenic origin. Specific Institute goals are to:

- Elucidate the fundamental, biochemical, and cellular mechanisms involved in myocardial ischemia and gain a better understanding of the systemic effects of cardiogenic shock.
- Develop methods for protecting ischemic myocardium and for preventing the conversion of reversible ischemic tissue to irreversibly infarcted and scarred myocardium.
- Develop methods for quantifying the extent of ischemic myocardium to aid the assessment of therapeutic efficacy and patient management.
- Encourage greater research effort on the development and evaluation of new drugs with a positive ionotropic action.

Planned Activities

Laboratory and clinical studies that focus on the cellular factors leading to death of heart muscle; efforts to quantify the extent of heart muscle inadequately perfused or irreversibly damaged following a heart attack; and development of methods to minimize the extent of heart muscle damage in heart attack.

Congenital and Rheumatic Heart Diseases

Program Goals

Congenital and rheumatic heart diseases typically become manifest in childhood or young adulthood. Diagnostic and surgical techniques have brought about great advances in the saving of life and improving the quality of life for afflicted individuals. Prevention efforts have made great strides against rheumatic heart disease, but only a few causes of congenital heart disease are understood, and few cases can be prevented. This brings into focus the value and importance of prevention, and the key is

the elucidation of fundamental causes and mechanisms. Thus, during the next 5 years, the Institute's research program will be directed toward achieving the following goals:

- Understand more fully the etiology of congenital heart defects.
- Improve surgical techniques for repair of defects and noninvasive techniques for diagnosis and treatment of patients with congenital and rheumatic heart defects.
- Seek better understanding of the developmental biology of the heart and the causes of, and/or susceptibility to, congenital and rheumatic heart disease.

Planned Activities

Studies on etiology of congenital heart disease; research on animal models; and study of the immunological problems in heart disease and their management, specifically in relation to rheumatic heart disease.

Cardiomyopathies and Infections of the Heart

Program Goals

The goals of this program area over the next 5 years are to:

- Encourage greater research effort on the causes and treatment of cardiomyopathies and infections of the heart.
- Develop more effective methods for diagnosis and treatment.

Planned Activities

Experimental work to study this disease; and investigation of animal models of several types of cardiomyopathy.

Circulatory Assistance

Program Goals

Depending on the extent to which cardiac function is compromised, circulatory assist devices may be required to relieve, in varying degrees, the workload of the heart or to perform the entire pumping function in place of the heart. The kinds of devices that may be suitable depend not only on the degree of cardiac function which must be restored but also on the time span during which such life-saving support is required. Thus, the broad goal of the Institute in this program area is to develop and test short-, intermediate-, and long-term circulatory assist devices for clinical use. Specific goals include:

- Investigate and assess components for circulatory-assist systems, such as blood pumps, engines, and control systems.
- Investigate and assess biocompatible materials suitable for circulatory-assist and other cardiovascular device applications.
- Extensively bench and animal test circulatory-assist devices, particularly of the left ventricular assist type.
- Conduct clinical evaluations for assessing the efficacy of, and defining the clinical indications for, left ventricular assist devices.

Planned Activities

Research, development, and evaluation of short- and extended-term implantable heart devices and power sources; clinical evaluation of temporary left ventricular assist devices directed at the short-term management of heart failure and shock.

Lung Diseases

Lung diseases and diseases of the respiratory system are a severe health problem. They account for over 5 percent of the years of life lost to illness and exact a huge toll in sickness, treatment requirements, and lost workdays. Respiratory diseases are the most frequent reasons that people seek a physician's attention; they account for more than 20 percent of all physician contacts and 12 percent of all short-term hospital stays. There are more lost workdays from respiratory disorders than any other category of illness.

The National Program is concerned with six major areas related to lung disorders: structure and function of the lung, emphysema and chronic bronchitis (chronic obstructive lung disease), pediatric pulmonary disease, fibrotic and immunologic lung diseases, respiratory failure, and pulmonary vascular diseases.

The National Program addresses these problems through the support of investigator-initiated research grants, contracts, intramural studies, and research training in lung diseases. The Specialized Centers of Research (SCOR's) in pulmonary diseases contribute strongly to the effort, and the overall Program stresses basic research, targeted research, clinical trials, demonstrations, technology development, and application of research findings.

Structure and Function of the Lung

Program Goals

The overall goals for the Institute in this area are to increase knowledge and understanding of the biochemical, physiological, immunological, and cell biological events that occur in the developing and adult normal respiratory system, and to determine how these are altered prior to clinical onset and during the course of pulmonary disease. The specific goals by which this mission will be accomplished are as follows:

Respiratory Function

- Improve understanding of gas exchange and transport, and of alterations associated with

exercise, high altitude hyperbaria, and disease states.

- Elucidate the respiratory mechanics in normal breathing, during physiological adjustments to exercise and altered environments, and in disease states.
- Increase knowledge of the roles of chemical, mechanical, and neural factors in the control of ventilation, and of adjustments during exercise, sojourn at high altitude, in sleep, and in the course of pulmonary disease.

Nonrespiratory Function

- Elucidate the roles of lung cells, enzymes, hormones, and immunological reactions in the defense of the lung against insults, both exogenous and endogenous, and disease.
- Improve understanding of the synthesis, secretion, and degradation of pulmonary surface-active material and its role in respiratory function of the normal and diseased lung.

Lung Structure

- Characterize the structural and functional features of various types of lung cells, interrelationships among different cell types, and modifications associated with lung injury and disease.
- Characterize the chemical and structural features of lung connective tissue components and alterations in the course of pulmonary disease.

Lung Growth and Development

- Increase knowledge of structural and functional changes during pre- and postnatal lung growth and development, and of the effects of endogenous and exogenous factors.

Planned Activities

Development of methods to separate major types of lung cells and determine the ultrastructural and biochemical characteristics of individual lung cells; studies of the mechanisms of lung tissue damage and repair; studies of intermediary metabolism of lung; and studies of basic lung physiology, the role of chemical, mechanical, and neural mechanisms in the control of ventilation, and the processes of gas exchange in the immature and the mature lung in health and disease.

Chronic Obstructive Lung Diseases (Emphysema and Chronic Bronchitis)

Program Goals

The Institute's program seeks means to prevent diseases through improved understanding of their causes; to delay or reverse disease progression through greater knowledge of pathogenesis; and to ameliorate disease effects through improved techniques for early diagnosis and more effective management. Specific goals to be achieved during the next 5-year period are:

Chronic Obstructive Lung Diseases

- Elucidate the basic mechanisms involved in structural and functional derangements associated with onset and progression of chronic bronchitis and emphysema.
- Improve the management of chronic obstructive lung diseases through identification of presymptomatic stages, critical assessment of current therapeutic measures, and development of more effective regimens.
- Prevent chronic obstructive lung diseases through understanding of individual risk factors, and their interactions and roles in the etiology and pathogenesis of these disorders.

Asthma

- Elucidate the underlying mechanisms in bronchoconstriction and development of more effective measures to ameliorate or prevent the bronchostrictor response.

Planned Activities

Studies of the natural history of PiZZ emphysema (a rare genetically related form of emphysema); studies to correlate biochemical and physiological alterations in early stages of chronic obstructive lung diseases; and clinical trials to study the use of intermittent positive pressure breathing for treatment of chronic obstructive lung disease.

Pediatric Pulmonary Diseases

Program Goals

Working toward the prevention of pediatric pulmonary diseases through increased knowledge of the underlying disease process, the Institute plans to achieve the following specific goals during the next 5-year period:

Neonatal Respiratory Distress Syndrome

- Improve the detection, management, and prevention of neonatal respiratory distress syndrome.

Bronchiolitis

- Increase the understanding of the relationship between bronchiolitis in childhood and subsequent disorders of the respiratory system.

Cystic Fibrosis

- Improve the identification of the basic defect and early pathogenetic changes through study of structural and functional derangements.
- Improve the management of cystic fibrosis through critical assessment of current modes of therapy and development of new regimens.

Planned Activities

Investigations to characterize the clinical, pathological, physiological, biochemical, and molecular events associated with normal lung development

and with the onset and course of hyaline membrane disease; and a Specialized Centers of Research program announcement encouraging applications for competitive funding for research projects in cystic fibrosis and bronchiolitis.

Fibrotic and Immunologic Interstitial Lung Diseases

Program Goals

The overall goals of the Institute in this category of lung diseases are to prevent interstitial lung diseases through better understanding of their causes and pathogenesis and to ameliorate their effects through improved diagnosis and management. Specific goals during the next 5 years are as follows:

- Elucidate the roles of immunologic and other basic mechanisms in the onset of interstitial lung diseases and the progressive changes that lead to pulmonary fibrosis and granulomatous lesions.
- Prevent and improve the management of interstitial lung diseases through identification of etiologic agents and other risk factors, early detection of disease, and development and improvement of therapeutic regimens.

Planned Activities

Investigations of specific agents responsible for fibrotic lung diseases in occupational environments, with specific attention to dose-response relationships; and investigations relative to the immunological and biochemical responses to organic and inorganic dusts that lead to fibrotic lung diseases and hypersensitivity pneumonitis.

Respiratory Failure

Program Goals

To reduce death and disability from respiratory failure, the Institute's overall goal is to improve the diagnosis, management, and prevention of adult respiratory failure through better understanding of the structural, biochemical, immunological, and physiological mechanisms of acute lung injury and repair. Specific goals directing the Institute's program during the next 5 years are as follows:

- Elucidate the intrinsic mechanisms involved in lung injury and the analysis of progressive changes that result in respiratory failure.
- Improve the therapeutic management of respiratory failure and development of measures that identify, arrest, or reverse degenerative changes accompanying lung injury.

Planned Activities

Studies to elucidate the basic mechanisms of the adult respiratory distress syndrome; and studies to determine how degenerative changes in the lung can be arrested and reversed.

Pulmonary Vascular Diseases

Program Goals

In pulmonary vascular diseases, early detection is the key to effective patient management, as increased fundamental knowledge of pulmonary circulation is to effective disease prevention. The overall goals of the Institute with respect to these diseases are to elucidate mechanisms regulating both normal and diseased pulmonary circulation to improve understanding of the pathogenesis of pulmonary edema, pulmonary hypertension, cor pulmonale, and pulmonary embolism and to bring this knowledge to bear on improving the diagnosis and treatment of these disorders. Specific goals for the next 5 years are as follows:

- Prevent pulmonary edema through understanding of mechanisms involved in the hydrostatic and permeability changes that affect fluid and electrolyte exchange in the lung.
- Elucidate the mechanisms controlling the normal pulmonary circulation and their relationship to the pathogenesis of pulmonary hypertension.
- Improve the management of pulmonary vascular diseases through development of noninvasive diagnostic techniques and more effective therapeutic regimens.

Planned Activities

Development of noninvasive techniques for early detection and continuous monitoring of pulmonary hypertension and pulmonary edema; and investigation of the structural, biochemical, and physiological characteristics of pulmonary vascular smooth muscle.

Blood Diseases and Blood Resources

Disorders of the blood are closely related to heart, blood vessel, and lung diseases. Blood is the vehicle by which oxygen, nutrients, and other body chemicals are carried to every part of the body to be exchanged for carbon dioxide, waste products, and chemicals which in turn need to be transported away from the tissues to other body organs either for excretion from the body or for use in the life processes.

The National Program is concerned with four major areas of activity related to blood: bleeding and clotting disorders, disorders of the red blood cell, sickle cell disease, and blood resources.

The National Program addresses these problems through investigator-initiated research, Specialized Centers of Research, contract studies in special areas of research and development, training programs, and programs to communicate the most current advanced knowledge to the public and to the practitioner.

Bleeding and Clotting Disorders

Program Goals

Advances in basic understanding of the coagulation system are critical to reduction of the incidence of disability and death from occlusive arterial and venous thrombosis, to the alleviation of symptoms of hemophilia and other bleeding syndromes, and to the development of effective therapies for congenital and acquired platelet disorders. To make these therapeutic improvements a practical clinical reality, the Institute has established six basic goals to guide its research activities for the next 5 years:

- Improve the diagnosis of, and therapy for, arterial thrombosis and the various clinical sequelae of this disease process; increase our understanding of the pathophysiology of arterial thrombosis to bring about its ultimate prevention.
- Enhance the knowledge of the basic mechanisms of venous thrombosis so as to provide improved patient care.
- Develop better understanding of the genetic and pathological mechanisms underlying hemophilia and other bleeding disorders to develop improved diagnostic techniques and specific treatments.
- Develop better methods for identifying and detecting individuals at risk for acquired coagulation disorders.
- Increase the general understanding of the role of platelets in the mechanisms of bleeding and clotting and develop more effective therapy for individuals suffering from congenital and acquired platelet disorders.
- Explore the pharmacology of agents such as the prostaglandins, aspirin, and oral contraceptives, which affect platelet interactions, endothelial function, and cellular reactivity to a variety of stresses.

Planned Activities

Investigations of the structure and function of coagulation factors and their *in vivo* regulators or inhibitors; further study of prostaglandins and thromboxanes to determine how platelet function is controlled; a broad range of studies to understand the thrombotic process and improve ability to prevent and treat thrombotic disorders.

Red Blood Cell Disorders

Program Goals

The overall goal of the program for the next 5 years is the development of new knowledge leading to reduced morbidity and mortality for those afflicted with thalassemia, aplastic anemia, and refractory anemia as well as various hemolytic anemias. Specific goals are to:

- Devise improved treatment for those afflicted with thalassemia. Major effort will be devoted to development and testing of techniques for prenatal diagnosis.
- Develop an understanding of factors controlling bone marrow proliferation and differentiation; develop knowledge of the underlying causes of aplastic and refractory anemias to permit prevention and improved treatment; and develop information concerning the natural history of these diseases.
- Further elucidate red cell membrane structure and function as well as intracellular metabolism to provide information which may be utilized to improve the health status of patients afflicted with various hemolytic anemias.
- Improve overall knowledge of the crucial role of the red blood cell in oxygen transport through studies of the mechanisms that control oxygen exchange.
- Develop erythropoietin (one of the prime regulators of red blood cell production) preparations suitable for use in controlling human diseases.

Planned Activities

Studies of the molecular and clinical aspects of thalassemia; purification of erythropoietin; and studies of the red blood cell membranes.

Sickle Cell Disease

Program Goals

To fulfill its mission to reduce morbidity and mortality due to sickle cell disease, the NHLBI has established the following goals:

- Continue basic research into the pathophysiology of the disease process at the molecular, cellular, and clinical levels.
- Develop improved methods of clinical care.
- Develop a more rational approach to patient management based on the latest scientific advances.
- Provide accurate, up-to-date information to health care providers and consumers.
- Evaluate the effectiveness of education, testing, and counseling programs.

Planned Activities

Studies of the conversion of fetal hemoglobin synthesis to adult hemoglobin production; molecular studies of globin gene expression at the alpha, beta, and gamma loci; studies on the metabolism of sickled cells and the role of coagulation in vaso-occlusive crises; collaborative studies to identify and evaluate the factors which determine the clinical course of sickle cell disease and the presence or absence of complications; development of new

drugs for the treatment of sickle cell disease; activities in educational, diagnostic, and counseling services in sickle cell disease, training, and community demonstrations.

Blood Resources

Program Goals

The mission of the NHLBI in the area of blood resources is directly related to the National Blood Policy objective of an adequate supply of high-quality blood and blood products. In pursuit of this objective, the Blood Resources and Transplantation Branch supports research in the areas of donor and recipient safety, blood substitutes, blood component therapy, transplantation biology, and all aspects of the management of blood resources, including collection, preservation, fractionation, and distribution.

Blood Resource Management

- Foster the efficient use and assure an adequate supply of high-quality blood and blood products for everyone in need.
- Promote more effective planning in the management of the national blood resource through the collection and analysis of national blood resource data.
- Encourage improved blood resources sharing both regionally and nationally.

Blood Safety Program

- Prevent morbidity and mortality from post-transfusion hepatitis and other transfusion-transmitted infections.
- Promote basic investigations centering on immunohematologic problems related to safety of blood therapy, particularly on different aspects of blood group antigens and antibodies, the Rh complex, and red cell antibody and complement interactions.
- Promote studies that will lead to greater safety for donors of blood and blood components.

Blood Substitutes Program

- Pursue further development of newly synthesized fluorocarbon compounds for use as blood substitutes in transfusion therapy, organ perfusion, and other promising areas of application, through screening and biological testing with the goal of clinical investigations into their usefulness in human medicine.

Blood Component Therapy Program

- Develop definite guidelines for the clinical use of blood components, including packed red cells, granulocytes, and platelet concentrates, for transfusion.
- Determine and clarify parameters for collection and storage of leukocytes as related to effective transfusion therapy; explore use of buffy coat as a source of human interferon.
- Develop new methods of plasma fractionation including the preparation of clinically useful trace components. Support clinical trials to establish the effects and role of these new components and methods.

Transplantation Biology Program

- Support fundamental research in immunology, immunogenetics, and other aspects of transplantation biology.

Planned Activities

Implementation of a national blood data center; evaluation of the impact of adenine on blood banking; development of specific and sensitive serological tests for the detection of non-A, non-B hepatitis carriers; support of studies to elucidate the immunopathogenesis of the hepatitis chronic carrier state; prospective analysis of trends in the incidence and etiology of transfusion-transmitted hepatitis; support of facilities for breeding and maintaining chimpanzees for use in hepatitis research; formulation and biological study of new fluorochemicals that have been previously screened for toxicity and suitability for blood substitution; research on the isolation and characterization of plasma proteins that have potential for new therapeutic uses; development of improved methods for producing human leukocyte interferon; and support of various research and demonstration projects at regional blood centers.

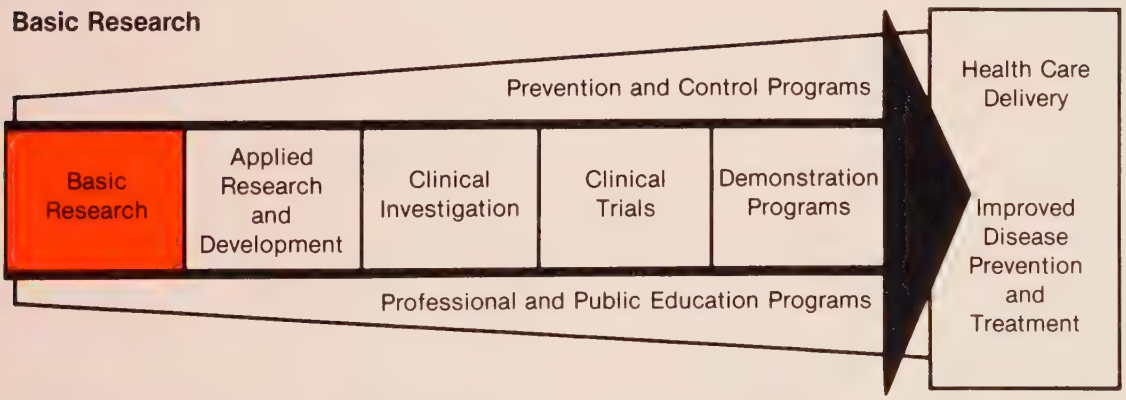
4

Highlights and Accomplishments:

Reflecting the March of Science

Echoing the sentiments of scientists over the centuries, Maurice B. Strauss wrote in 1964, "Discoveries do not arise *de novo*, like Athene from the brow of Zeus, but are akin to the living layers of a coral reef built on the past labors of countless predecessors." Certainly, giving due credit to the individual labors of the legion of workers in heart, lung, and blood diseases during the past year alone would be an unattainable task, even in a volume many times the size of this report. But the unfailing contributions of this dedicated corps of investigators, largely anonymous to the public, keep the march of science unmistakably forward. From basic researchers in the laboratory to participants in prevention, education, and control programs, scientists in diverse settings across the Nation quietly accumulate the bed of facts on which the intuitions of discovery rest.

Unavoidably, the highlights and accomplishments presented in this section offer the reader only a glimpse of progress made over the past year through activities initiated or supported by NHLBI. Descriptions of selected advances are punctuated by phrases such as "may help explain . . . ," "raise the possibility that . . .," and "has potential implications for . . .," underscoring the constant evolution and refinement of biomedical knowledge. At times the harvest of this research continuum is distinct and pragmatic: the usable process, the medicine, the machine. More often, however, its fruit is less tangible but equally critical: understanding. For in the words of Rene Dubos, "The immense wastefulness of organic life, which demands that thousands of germs perish so that one may live, has its counterpart in the processes of intellectual life; many must run, so that one or a few may reach the goal."



Basic research is a systematic, intensive effort directed toward greater knowledge or understanding of the subject studied.

Within biomedicine, basic research deals with the structure and function of molecules, organelles, cells, tissues, organisms, and populations of man—or of suitable nonhuman models—in health and disease.

As the foundation of the Institute's program, basic research on disease etiology and pathogenesis receives the major portion of Institute resources. This research has resulted in a number of significant concepts, theories, and discoveries which, in turn, have become the foundation for further research, refinement, development, evaluation, and dissemination to the medical community and the public.

Atherosclerosis
—Improved understanding of low density lipoprotein degradation

Cholesterol has a substantial role in the development of atherosclerosis or blockage of the blood vessels. Low density lipoprotein is the major vehicle whereby cholesterol is transported in human blood plasma. Over the past few years scientists have found that a number of cultured human cells, such as fibroblasts, arterial smooth muscle cells, lymphoid cells, and endothelial cells, have a common pathway for degrading low density lipoprotein. In this pathway LDL is first bound to a high affinity receptor on the cell, an ordered sequence of biochemical processes takes place, and the release of free cholesterol for use by the cells results. Receptor recognition in the cells appears to develop on certain functionally significant arginyl residues on the LDL apoprotein. However, this had not been demonstrated *in vivo*.

Recently, *in vivo* studies have confirmed the importance of this pathway for LDL catabolism. These studies have demonstrated that the plasma clearance rate of LDL is affected by chemical modification of the arginyl residues on LDL apoprotein. This finding indicates that the specific receptor binding mechanism plays an important role in LDL degradation. Findings such as these may eventually allow clinical applications to control the cholesterol levels in the bloodstream.

Atherosclerosis
—Platelet-vessel wall interactions

Platelets secrete a granular protein that initiates proliferation of myointimal cells (forming the innermost muscle layer in the blood vessels) following vascular injury. Platelet-vessel interactions and the fate of secreted granules following intimal injury with an intravascular balloon were analyzed by measuring platelet Factor IV in the plasma and vessel walls during infusion of PGI_2. Plasma levels of Factor IV measured by radioimmunoassay did not increase beyond the normal range following the injury, but Factor IV was detected in the vessel wall by indirect immunofluorescence. Following the administration of graded doses of PGI_2, platelet aggregation and adhesion were almost totally inhibited and the entry of Factor IV into the vessel wall was prevented.

These studies provide the first definitive proof that secreted platelet granule proteins enter the vessel wall as well as demonstrating that PGI_2 infusion can block platelet adhesion to the vessel wall. These studies may provide a means for monitoring and preventing platelet interactions with injured vessels that may ultimately lead to atherosclerotic vascular disease.

Atherosclerosis
—Foam cell development in familial hypercholesterolemia

A characteristic feature of the lipid-rich forms of atherosclerotic plaques is the presence of lipid-engorged cells or foam cells derived from macrophages and from smooth muscle cells in the arterial intima. The detailed mechanism by which these cells accumulate lipid is not known. The receptor mechanism of normal low density lipoprotein utilization does not explain foam cell development and hence does not explain this important aspect of plaque pathogenesis.

A major insight into the mechanism for excessive deposition of cholesterol in tissues and arteries of individuals with homozygous familial hypercholesterolemia has been obtained from studies with mouse peritoneal macrophages. The observation that the macrophages distributed throughout tissues of familial hypercholesterolemia subjects show a marked deposition of LDL-derived cholesterol esters in the absence of a high affinity receptor of LDL may now be explained by the demonstration in the mouse macrophage of a modified mechanism for the uptake of LDL and the regulation and accumulation of cellular cholesterol. The mouse cell contains a binding site that recognizes LDL and lipoproteins which have been chemically modified and internalizes and degrades the altered molecules. Electron microscopy has shown that the esters are stored in cytoplasmic droplets which are not surrounded by a membrane and that the lipid-laden mouse macrophage resembles the foam cells seen in the xanthomas and arteries of familial hypercholesterolemia subjects.

The finding of binding sites for modified lipoproteins or macrophages may well explain the development of macrophage foam cells in plaques in patients with familial hypercholesterolemia.

Hypertension
—New evidence that plasma kallikrein plays a role in the activation of prorenin

Renin appears to play an important role in controlling blood pressure by initiating a reaction that finally leads to the production of the vasoconstrictor peptide, angiotensin II. It has recently been shown that normal human plasma contains a higher molecular weight form of renin (prorenin) which is enzymatically inactive. *In vitro* prorenin is converted to active renin by acid activation or the addition of trypsin or pepsin. Recently, it has also been shown that serine proteases may be involved in the activation of prorenin. Furthermore, human urinary kallikrein also activates prorenin when added to plasma in small concentrations. Therefore, scientists have hypothesized that kallikrein may be the substance which activates prorenin *in vivo*. The most recent findings suggest that plasma kallikrein may indeed be a physiological activator of prorenin, but they do not support a role for urinary kallikrein.

Hypertension

—Studies clarify the role of the prostaglandins in renin regulation and other processes related to hypertension

Renin is a substance that is produced in the kidneys and appears to have a major role in regulating blood pressure. It is known that varying levels of renin in the bloodstream are correlated to variations in blood pressure, but it has not been fully known how renin secretion is stimulated or inhibited. Recent findings suggest that the prostaglandins stimulate the release of renin from the kidney and augment the steroidogenic effects of angiotensin II and angiotensin III in the adrenal cortex.

Recent animal studies have characterized the effects of two inhibitors of prostaglandin excretion on the production of prostaglandins. It has been shown that both indomethacin and mecloferamate decrease adrenal prostaglandular synthesis and reduce the release of renin. Angiotension II and III have been shown to increase serum aldosterone. Current data indicate that inhibitors of prostaglandin synthesis influence the renin-angiotensin-aldosterone not only by decreasing the release of renin, but also by reducing angiotensin-induced aldosterone release. Tissue prostaglandins appear to be involved in controlling the release of renin, modulating or mediating angiotensin II and III steroidogenesis, antagonizing the vasoconstrictor action of angiotensin II, and modulating the effect of aldosterone on sodium transport.

Hypertension

—Development of prostaglandin antagonists

Although research on prostaglandins in the cardiovascular area has increased significantly in recent years, the prostaglandins' role in hypertension and blood pressure regulation remains unknown. Research findings thus far seem to indicate that PGA_2, PGE_2, and PGF_2 (prostacyclin) act as vasodilators, whereas PGH_2 and TA_2 (thromboxane A_2) act as vasoconstrictors. The prostaglandins seem to affect the circulation by serving as local mediators of hormone systems that are vasoactive, e.g., bradykinin, angiotensin II, etc. The complex nature of prostaglandin chemistry and the lack of specific prostaglandin antagonists make it virtually impossible to define the role of compounds in hypertension and blood pressure regulation. However, several investigators have recently reported the *in vitro* antagonist/agonist activity of the unsaturated fatty acid 5,8,11,14,17-eicosapentaenoic acid (EPA), an arachidonic acid analog. Not only does this compound inhibit the metabolism of arachidonic acid, but it also potentiates the formation of triene prostaglandins (PGH_3, PGI_3, and TA_3), inhibitors of human platelet aggregation. In so doing, the formation of thromboxane A_2, a potent human platelet aggregator and vasoconstrictor, is curtailed. The precise nature of the effects of specific prostaglandins and the magnitude of these effects on blood pressure regulation and hypertension are not clear; however, continued research and development of prostaglandin antagonists may form the basis for future hypertension therapy.

Hypertension

—Link to red cell transport abnormalities

Because of their availability and ease of manipulation, red cells have long been a favorite subject for studies of membrane structure and function, and many transport pathways have been identified in the red cell. Recently, two studies have shown that under special conditions *in vitro,* abnormal cation movement can be demonstrated in the red cells of patients with essential hypertension. The studies report that red cells of hypertensive patients exchange lithium for sodium more rapidly than normal. Another study reports a low ratio of sodium extrusion to potassium uptake in red cells preincubated to reduce the normal transmembrane gradients for these ions. It has been suggested that observations such as these may lead to the development of screening techniques to identify the 9 percent of the general population that has or is destined to develop secondary hypertension, and it seems worthwhile to administer such tests to hypertensive patients and their relatives. One study, for example, found that in first-degree relatives of eight patients with essential hypertension, the rate of sodium-lithium countertransport was higher than in controls. The pathophysiologic implications of these findings remain to be clarified, as a direct causal relationship between red cell ion transport and hypertension seems unlikely.

Ischemic Heart Disease

—The effect of the complement system on myocardial infarct size

The cellular and subcellular processes that cause irreversible damage to myocardial cells after an ischemic event are not well-defined. Information on the event or series of events that determine the onset of irreversible ischemic damage would be extremely useful in the development of therapies aimed at limiting the size and extent of a myocardial infarction. Using a baboon model of experimental myocardial infarction, a team of researchers has demonstrated that baboons that have been totally depleted of the third component of the complement system (C3) have significantly smaller infarcts than those that were not depleted of C3. It was also found that the effect of limitation of infarct size was most pronounced in an anatomic region known as the "border zone," the region most likely to be salvaged by therapeutic intervention. Since complement is part of the immunologic system of the body, and since it has been demonstrated that the baboon complement system is immunologically indistinguishable from that of humans, these results may provide the rationale for using steroids and nonsteroidal anti-inflammatory drugs in the

treatment of the acute stages of myocardial infarction.

Cardiac Arrhythmias

—Valve muscle may be site of origin of arrhythmias

It has been found that the electrical potentials of heart valve muscle and the atrioventricular node are similar. Moreover, in studies examining dogs and apes, valve muscle has generated impulses in the presence of catecholamines. This evidence suggests that the heart valve may be the site of origin of some atrial arrhythmias. The ultrastructure and electrophysiology of a mitral valve leaflet obtained from the heart of a cardiac transplant recipient was studied, and it was found that the valve contained atrial muscle in direct continuity with the left atrial myocardium. In the absence of electrical stimulation, the valve muscle depolarized and initiated impulses at a slow rate automatically, and the rate of impulse generation was increased by epinephrine. The results of these studies indicate that cardiac muscle in the human mitral valve can initiate impulses and thus might be a site of origin of arrhythmias in the human heart.

Sudden Cardiac Death

—Contribution of psychological stress to ventricular fibrillation

For some time it has been thought that psychological stress increases the vulnerability of ischemic myocardium to ventricular fibrillation, although the mechanism by which this occurs remains obscure. In studies using psychologically stressed, conscious animals, it has been shown that cryogenic blockade of certain areas of the brain (forebrain, dorsolateral hypothalamus, fields of Forel) would prevent the occurrence of ventricular fibrillation following coronary artery occlusion. These findings are consistent with the view that coronary artery obstruction alone is not sufficient to elicit ventricular fibrillation and death. The integrity of neural pathways may mediate the cerebral effects of stress to the myocardium and may be necessary for the initiation of ventricular fibrillation. If a pharmacologic agent that mimics this neural blockade could be developed, ventricular fibrillation could be prevented in cases where coronary artery disease has placed the patient at high risk for sudden cardiac death.

Cystic Fibrosis

—Defective host mechanism found responsible for susceptibility of lung infections

Although cystic fibrosis is a systemic disease, pulmonary infections are the most common cause of morbidity and mortality. Cystic fibrosis patients are particularly susceptible to pulmonary infections by an organism—*Pseudomonas aeruginosa*—that is ubiquitous in the environment but is usually not pathogenic in healthy individuals. Of patients with cystic fibrosis, 70 to 90 percent are found to have mucoid colonies of this organism; such colonies are rarely observed in other human disease states.

A recently completed study suggests that inhibition of the defense mechanism that is provided by the pulmonary alveolar macrophage may be the basis of the unusual susceptibility of cystic fibrosis patients to infections from *P. aeruginosa*. Serum samples from 49 patients were studied for their effect on phagocytosis of various pathogens by the alveolar macrophage. Forty of these patients showed 60 percent or greater inhibition phagocytosis of *P. aeruginosa*, but not of *Staphylococcus aureus* or *Serratia marcescens*. Moreover, mixing the cystic fibrosis serum with normal serum did not overcome the inhibitory effect, nor was the effect lost upon exposure of the serum to glass, upon freezing, or upon heating to 56 °C for 30 minutes.

These *in vitro* studies suggest that the serum of cystic fibrosis patients may contain a factor that compromises the *in vivo* control of infection in these subjects. As cystic fibrosis patients are known to have elevated levels of antibodies to *P. aeruginosa* in both their serum and pulmonary secretions, these recent observations on the pulmonary alveolar macrophage suggest that to a certain extent this phagocytic defense system functions independently of the systemic humoral and cell mediated immune systems.

Because mucociliary transport is known to be impaired in cystic fibrosis patients, the phagocytic action of the alveolar macrophage in clearing bacteria becomes more important than in normal subjects with adequate mucociliary transport.

Since not all sera from cystic fibrosis patients exhibit this inhibition of the alveolar macrophage, it is suggested that the phenomenon may not be an intrinsic defect in cystic fibrosis, but rather an acquired alteration in the patients' defense system. Studies are in progress to elucidate the mechanisms underlying this aspect of the host defense.

Idiopathic Pulmonary Fibrosis

—Collagenase as a potential diagnostic tool

Idiopathic pulmonary fibrosis is a usually fatal disorder of the lung which is characterized by chronic inflammation of the alveolar structures and progressive interstitial fibrosis. Despite a considerable research effort directed toward understanding this disease, minimal advance has been made in elucidating initiating events and pathogenetic mechanisms involved. Recently, however, analysis of bronchial lavage samples from patients with this disorder has revealed the presence of significant quantities of collagenase, an enzyme capable of digesting collagen, one of the basic structural proteins of the lung. The enzyme was not found in lung washings from normal individuals. Since idiopathic pulmonary fibrosis is a disorder of unknown etiology, the possibility that the

presence of collagenase may be a diagnostic tool is of considerable interest. It also suggests that idiopathic pulmonary fibrosis may be caused by degradation of collagen in the lung that is followed by disordered resynthesis, and that the enzyme collagenase may be useful in monitoring the disease process.

Von Willebrand's Disease
—Inhibition of factor-dependent platelet function by prostacyclin

Von Willebrand's disease is a congenital hemorrhagic disorder characterized by platelet defects or deficiencies in blood coagulation Factors VIII or IX. In this disorder, prostacyclin is thought to inhibit platelet function by increasing cyclic AMP (cAMP), a cell membrane nucleotide that plays a key role in the biochemical action of a number of hormones. In turn, cAMP blocks thromboxane synthesis and release. However, it was recently shown that prostaglandin E_1, which also increases cAMP, and dibutyryl cAMP can inhibit von Willebrand factor-dependent platelet aggregation by another mechanism.

To expand on this observation, the effect of prostacyclin on human and bovine von Willebrand factor-dependent function was studied in three different systems. Results suggest that prostacyclin inhibits factor-dependent platelet function by altering the platelet membrane and reducing factor binding. This could account for prostacyclin's inhibition of platelet adhesion to subendothelium, which may contribute to the inhibition of the development of atherosclerosis.

Clotting Disorders
—Thromboxane production in endothelial cells

Endothelial cells constitute a one-cell-thick inner lining on the walls of all blood vessels. It was recently discovered that these cells produce thromboxane, a substance that can cause platelet clumping and blood vessel constriction. Prior to this discovery, it was thought that only platelets in the cardiovascular system could make thromboxane and that endothelial cells produced mainly prostacyclin, a potent vasodilator and inhibitor of platelet aggregation. It is now realized that both platelets and endothelial cells can produce potent prostaglandins or thromboxanes, which can have either prothrombotic or antithrombotic effects and may be related to the etiology and pathogenesis of various hemolytic and thrombotic diseases.

Blood Coagulation
—Partial homology of antithrombin III with alpha-1-trypsin inhibitor

Antithrombin III is a single-chain plasma glycoprotein which inhibits thrombin and other serine proteases involved in blood coagulation. Inhibition involves the formation of a molecular complex of enzyme and inhibitor and the rate of complex formation, especially with thrombin, is greatly increased in the presence of heparin. The nearly complete amino acid sequence of human antithrombin was recently reported and is the first sequence of a plasma protease inhibitor to be identified. This sequence has been compared with the known sequences of the smaller trypsin inhibitors and also with the trypsin inhibitors from plants. No convincing sequence homology has been found; therefore, antithrombin seems to represent a new family of plasma inhibitor structures. As a consequence, no conclusions regarding the location and identity of its inhibitor site or its mechanism of action can be drawn from available knowledge. Comparison with the available data on the partial sequence on alpha-2-macroglobulin has so far failed to turn up any evidence for convincing sequence homology between antithrombin and alpha-2-macroglobulin. Because of the differences in heparin-binding specificity between antithrombin and platelet Factor IV, thrombin, and lipoprotein lipase, an understanding of the heparin-antithrombin interaction will probably require a tertiary structure determination of the complex itself.

The sequence of a fragment of alpha-1-antitrypsin has also been reported recently, and the antitrypsin fragment can be aligned with a portion of the antithrombin sequence. The degree of sequence identity (35 percent) is of the same order of magnitude as that observed between serine proteases and is clear evidence for a sequence homology.

One of the consequences of this sequence homology is that the mechanism of inhibition must almost certainly be the same for alpha-1-antitrypsin and antithrombin and that their inhibitor sites will engage corresponding residues in the two structures.

Thrombosis
—Explanation of molecular mechanisms by radioimmunoassay

A study of intravascular coagulation using disseminated intravascular coagulation as a model for *in vivo* thrombosis has provided clues to the intricate balance between blood clotting and fibrinolysis. The proteolysis of fibrinogen by thrombin was measured by several sensitive radioimmunoassays and, from the data obtained, it has been postulated that proteolysis of fibrin I is a major mechanism regulating the production of fibrin II, the form of fibrin that is released and converted to crosslinked fibrin polymers via Factor XIIIa. The balance between plasmin proteolysis of fibrin I or transformation into fibrin II is of major pathophysiological importance in determining whether fibrin I formation is accomplished by thrombosis. Measurement of both thrombin and plasmin action in plasma may thus help to identify those patients at greatest risk of developing clinical thrombosis.

Prostaglandin Synthesis

—Evidence of new pathway of arachidonate release

Human platelets contain large quantities of arachidonate, a precursor of prostaglandins, bound to phosphotides and released during platelet aggregation. It was previously believed that arachidonate was released through the action of a phospholipase A_2, cleaving arachidonate from phosphatidylcholine. There is now evidence for a new pathway that involves two enzymes, a phosphatidyl inositol-specific lipase C and a diacylglycerol lipase that releases arachidonic acid. In platelet stimulation studies, the activity of these two enzymes was sufficient to account for the flow of arachidonate.

The discovery of this new pathway provides the background for additional studies elucidating potential new inhibitors of prostaglandin synthesis and lipoxygenase action, and, if this function can be generalized to other tissues, approaches to developing new anti-inflammatory agents may be identified.

Red Blood Cell Disorders

—Progress toward gene insertion therapy

Suppression of bone marrow hematopoiesis is one of the main limitations to intensive treatment with most anticancer chemotherapeutic drugs. If the resistance of marrow cells could be enhanced by simple procedures, then higher doses of drugs could be used in the treatment of cancers of other tissues. Methotrexate is an anticancer drug that acts as a folic acid antagonist by inhibiting the enzyme dihydrofolate reductase. Resistance to methotrexate was induced in bone marrow cells of mice by transformation *in vitro* with DNA from a drug-resistant cell line. Transformed cells had elevated levels of dihydrofolate reductase and demonstrated a proliferative advantage over untransformed cells.

This gene insertion procedure did not have any adverse effects on the recipient mice, an important observation if one considers the potential clinical applications in humans. The hemoglobinopathies, such as thalassemia and sickle cell anemia, would appear to be natural targets for treatment by gene transfer techniques. Currently, no curative treatment in these disorders exists. Their primary defect resides at the level of the host DNA and is manifested in hematopoietic tissues that continue to proliferate throughout life. Insertion of a normally regulated and structurally normal beta-globin gene should, in theory, correct the defects in Cooley's anemia and sickle cell disease. However, since a normal beta-globin gene would not lend any proliferative advantage to the transformed marrow cells, it would appear necessary to link it in some manner to a gene whose expression is susceptible to selective pressures; drug-resistant genes are natural candidates for this role.

Sickle Cell Disease

—Animal model development for intravascular assays

Within the last few years, intensive study of sickle cell disease has provided vital information of critical value in human biology. At the molecular level, significant advances have been made in understanding the formation of the sickle hemoglobin gel, and to a lesser extent, the deformation of the sickle erythrocyte which follows deoxygenation. Yet there is almost no understanding of the mechanism by which such cellular changes lead to tissue damage and the ultimate pathophysiological manifestations of sickle cell disease. Several ways of studying the flow or rheological properties of sickle erythrocytes, including measures of viscosity, filterability, and deformation, have been used *in vitro*, but there are considerable technical problems with all these methods and the correlation of any one method with the others is not established. Progress in development of methods to improve the structure and functioning of defective or damaged erythrocytes has been inhibited because human subjects cannot be exposed to those experimental conditions known to induce sickling *in vitro*. A current study is developing primate models for study of the pathophysiology of sickle cell disease. Specifically, the recovery and survival of small quantities of ^{51}Cr-labeled human erythrocytes transfused to nonhuman primates were measured. In two chimpanzees, all the human erythrocytes circulated 15 minutes after transfusion and were subsequently removed from the animal's blood. In baboons and rhesus monkeys, over 95 percent of the human erythrocytes were cleared within 15 minutes after injection.

Hepatitis

—Development of serologic assay for non-A, non-B hepatitis

Non-A, non-B hepatitis is responsible for the vast majority of the remaining cases of transfusion-associated viral hepatitis. The most convincing evidence for non-A, non-B agents comes from prospective studies in blood recipients and from successful transmission of the disease to chimpanzees. Despite the availability of an experimental animal model, no viral agent has been identified which fulfills accepted serological criteria of an etiological agent.

Immune complexes circulate in a variety of inflammatory, infectious, and neoplastic diseases but particularly in liver diseases, where the antigenic component is usually unknown. Recently, it has been shown that circulating immune complexes are common in patients with non-A, non-B hepatitis and, because of the lack of progress in identifying a non-A, non-B viral antigen with more conventional approaches, the possibility that these immune complexes contain viral antigens is under investigation. Techniques to identify the antigenic

component of the immune complexes are being developed. This novel approach may lead to a long-awaited immunological marker for an agent which is responsible for most transfusion hepatitis and a high incidence of chronic liver disease after acute infection.

Hepatitis

—Development of better diagnostic methods

Recently, an elusive new soluble antigen—the *e* antigen—has been detected in persons who are positive for hepatitis B surface-antigen. Although understanding of this *e*-antigen system is still tenuous, antigen positivity has been linked to hepatitis infection and appears to better identify the truly infectious carriers. It has been suggested that the presence of *e* antigen in acute disease signals the eventual development of chronic liver disease. Nevertheless, the true nature of this antigen, whether viral or host specific; its role, if any, in the pathogenesis of hepatitis B infection; and its full clinical implications remain unclear. Therefore, the solution to this very intriguing problem depends upon the development of extremely sensitive and specific serologic methods.

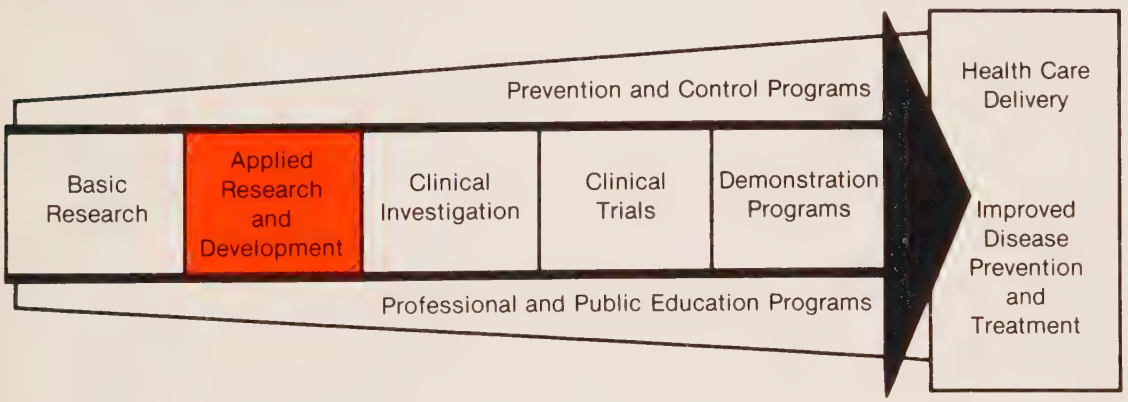
Research in transfusion-associated hepatitis has produced encouraging progress toward the realization of a radioimmunoassay test for the detection of *e* antigen and anti-*e* antibody. The test, based on a "universal" reagent, can also be applied to essentially all antigen-antibody systems. Preliminary studies employing this new assay indicate a greatly increased sensitivity, easier performance with reduced time, and lowered costs.

Blood Substitutes

—Development of stroma-free hemoglobin

Blood transfusion is frequently required to maintain adequate oxygen transport in anemia and to restore blood volume following hemorrhage from trauma or disease. At times when donor blood stores have been seriously depleted or when large quantities of typed and cross-matched blood are needed for patients undergoing major surgery, the availability of nonantigenic blood substitutes would be of great value in clinical practice. While different fluids have been used successfully in the past for plasma volume expansion, restoration or oxygen transport by these substitutes has been unsuccessful. Recently, rats were totally exchanged with a solution of pure (stroma-free) hemoglobin and were able to survive for several hours. Transfusion with stroma-free hemoglobin offers several advantages: hemoglobin complexes not only have oxygen affinities comparable to whole red blood cells but they remain in the circulation for longer periods of time; stroma-free hemoglobin does not need to be typed prior to use; and the risk of transmitting hepatitis is minimized. Blood substitutes have potential importance in clinical therapy as temporary replacements for whole blood. The availability of an effective substitute for red blood cells could modify blood bank management strategies designed to meet emergency situations as well as improve the efficiency of blood programs while improving cost effectiveness of patient care.

Applied Research and Development



Applied research is a systematic study directed toward applying new knowledge to meet a recognized need. In both the laboratory and clinical settings, applied research is aimed first at obtaining specific knowledge that will enable the investigator to judge whether it is feasible to produce a new or improved means of preventing, diagnosing, or treating a particular disease. Subsequently, new approaches and technologies can be developed. To accomplish these goals, applied research is dependent on the existence of a relevant scientific base of knowledge. From this foundation, applied researchers create a means to accomplish a specific practical goal.

Development is the systematic application of available knowledge which is directed toward the production of useful materials, devices, agents, and methods to meet a recognized need. It is a subset of applied research, sharing common goals. Developmental processes to achieve these goals include design, development, and improvement of prototypes and new processes to meet functional or economic requirements.

Coronary Heart Disease

—New technique for measuring the extent of infarction

Nuclear magnetic resonance (NMR) is being exploited as a technique to identify the chemical changes in the heart following infarction. This may provide a noninvasive method for quantitating the amount of "dead" myocardium following an infarct. Investigators working with an isolated rat heart have noted that the NMR phosphate peak shifts its position if the oxygen supply to the heart is interrupted. It returns to its normal position when the oxygen supply is restored. If the supply to only part of the heart is interrupted, two phosphate peaks appear. Investigators are now attempting to determine if the size of an infarct in such an isolated heart can be related to the size of the two phosphate peaks. Thus NMR has the potential of assessing the effectiveness of agents that may limit the extent of damage caused by an infarction. This noninvasive technique has the added advantage of not requiring the use of ionizing radiation.

Coronary Artery Disease

—Technique for noninvasive diagnosis

Previous studies have shown that noninvasive radionuclide cineangiography performed during exercise allows detection of abnormalities in heart function in patients with coronary artery disease. Recently, investigators have compared this technique to exercise cardiography in detecting coronary artery disease. The predictive accuracy of the radionuclide technique in a symptomatic population was high. Investigators judge that radionuclide cineangiography is more sensitive than electrocardiography, and is highly predictive and specific in detecting coronary artery disease.

Hypertension

—Purification of angiotensin I peptide

Renin is a proteolytic enzyme produced by the juxtaglomerular cells of the kidney. The juxtaglomerular cells function as baroreceptors, or blood pressure sensors, and release renin when there is a decrease in blood pressure or blood volume. Renin, in turn, releases angiotensin I which is converted to angiotensin II by a converting enzyme produced in the lung. Angiotensin II is the most potent vasoconstrictor of biological origin known and its release is immediately responsible for increasing systemic blood pressure. Hypertension, therefore, may be viewed as a disorder of the regulation of the renin-angiotensin system. Through an interagency agreement with the National Bureau of Standards, a convenient, high-resolution method of purifying a synthetic angiotensin I standard has been developed. This standard may be used in plasma renin activity assays which have broad application in research as well as in the diagnosis and treatment of hypertension. The purification method developed as a result of this work may also be applied to other synthetic peptides of biological interest and represents a significant improvement in available technology for the detection and characterization of hypertension.

Ischemic Heart Disease

—Review of new technique for treating coronary obstructions

Percutaneous transluminal coronary angioplasty is a new technique that has been developed with the goal of relieving the obstruction of the more proximal coronary arteries without coronary bypass surgery. In some ways, the procedure is similar to the diagnostic catheterization in which a fine tube is advanced from an arm or leg artery through the arterial system to the heart or into the coronary vessels. With transluminal coronary angioplasty, a special catheter is used which has a tiny balloon at its tip. The tip of the catheter is advanced into the artery that is narrowed, and the balloon is momentarily inflated at high pressure. This causes a forcible expansion and opening of the coronary narrowing. The balloon is then quickly deflated and the catheter withdrawn.

While this method offers promise, it is one with which there is incomplete research experience. As currently perceived, the technique is potentially applicable to patients with noncalcified narrowings restricted to the proximal portion of certain coronary arteries; such patients represent only a small fraction—estimated at less than 5 percent—of patients now undergoing coronary bypass surgery. To monitor the level of experience and report on possible benefits and adverse effects of this technique, NHLBI maintains an analytical registry of patients treated with PTCA.

Data have been collected from 23 centers in the United States and Europe performing PTCA since September 1977. Of the 291 patients who have undergone the procedure, 89 percent had single vessel disease, 8 percent had double or triple vessel disease, and 3 percent had left main coronary artery disease. PTCA was judged as a success in that coronary narrowing was decreased by at least 20 percent in 58 percent of the patients; the average narrowing was reduced 47 percent—from an obstruction of 82 percent to one of 35 percent.

Results show that PTCA can improve myocardial blood flow and performance in specifically

selected and prepared patients in the hands of an experienced team. They also show, however, that the technique involves a definite risk to the patient: 7 percent of the patients undergoing PTCA required emergency coronary bypass surgery, 3 percent suffered myocardial infarction, and 1 percent died in the hospital.

In general, these results from the NHLBI registry confirm the safety of PTCA in patients with single vessel coronary artery disease. Work is continuing to determine the role of this technique in patients with more extensive coronary artery disease.

Diagnostic Instrumentation —*Intravenous arteriography*

Conventional diagnostic methods for the assessment of symptomatic cardiovascular disease have depended on selective arteriography using photographic film and requiring catheterization to inject the radiopaque contrast agent. This procedure involves an attendant risk and an overnight hospital stay for the patient. After 5 years of development, a new intravenous angiographic system has been completed which can provide unusually high contrast X-ray images without catheterization, using intravenous injection of contrast agent and the electronic subtraction of images by a high speed digital computer system. The system is designed so that patients will require less than 1 hour per diagnostic procedure, receive a dose rate equal to or less than that of the conventional arteriographic method, and be examined as outpatients. Initial studies have utilized the system for imaging of the carotid, intracranial, and renal arteries, and the aorta as well as visualization of the heart and kidneys. This photoelectronic radiography method could have broad application in cardiovascular disease diagnosis because the images are processed electronically instead of on photographic film, and because of its benefits in terms of reduced risk to the patient and reduced cost.

Heart Failure —*Study of sea anemones yields promising medical products*

Since the introduction of digitalis some 190 years ago, the cardiac glycosides have remained the most important therapeutic agents for congestive heart failure. However, the incidence of digitalis intoxication is relatively high, and such toxicity can be lethal. Careful clinical judgment must be exercised in use of the glycosides since they have a low margin of safety in comparison to many drugs in the United States.

For some years, NHLBI-sponsored investigators have been screening peptides extracted from sea anemones of the Pacific for cardiotonic activity. Recently, three polypeptides (Anthopleurin A, B, and C) that exhibit cardiotonic (positive inotropic) actions were isolated; Anthopleurin-A appears to do so with a higher therapeutic index than cardiac glycosides. Essentially no other physiological effects even above the "effective dose—100 percent" (ED-100) for positive inotropic effect have been observed.

Recent progress in this area includes development of improved methodology to obtain 97 percent pure Anthopleurin-A in relatively large amounts; spectroscopic studies and sequencing of Anthopleurin-A; the finding that Anthopleurin-A is antigenic, but that C-reactive protein may block the antigenicity; initiation of fragmentation studies of Anthopleurin-A with pharmacologic screening of lower molecular weight fragments for cardiotonic activity and lack of antigenicity; and development of a method of "milking" the anemones to release polypeptides without damage to the organism, thus assuring adequate supply. These polypeptides show promise as potentially useful drugs in human heart failure. Pure samples are being provided to other researchers for further evaluation and to drug companies for development of injectable compounds.

Left Ventricular Failure —*Progress toward development of implantable left heart assist devices*

Left heart assist devices are intended to provide temporary circulatory support for postoperative cardiac surgical patients who have profound left ventricular failure and who cannot be weaned from cardiopulmonary bypass or who deteriorate into cardiogenic shock postoperatively. Clinical evaluation of the short-term use of these devices was undertaken after a great deal of rigorous animal experimentation, and they were shown to be both clinically safe and functionally effective. However, for long-term effectiveness, implanted cardiac assist devices require energy delivered from outside the body or the development of a fully implantable blood pump, energy converter, and electrical transmission system. Feasibility studies have recently been undertaken to test integrated blood pumps and electrical energy converters, and preliminary *in vitro* tests in calves have produced uniformly good results. Preliminary results from another program have also demonstrated the feasibility of transmitting electrical energy through the intact skin using a unique single turn transformer implanted as a belt around the torso of an animal. Electrical and mechanical integrity have been demonstrated for a period of 6 months and the device has accommodated passage of energy through the skin without causing infection or rejection of this device. Research and development of these devices will continue with the goal of achieving integrated ventricular assist systems that are ready for preclinical reliability testing for long-term use.

Chronic Obstructive Lung Disease
—Testing controversy resolved

The most widely used spirometric tests of ventilatory function are the FVC (forced vital capacity) and FEV_1 (forced expiratory volume in 1 second of expiration), which are used to indicate the presence of airway obstruction and to follow its course. Both types of measurement can be obtained from one simple maneuver in which the subject exhales into the spirometer, emptying the lung as quickly and completely as possible after inhaling to maximum capacity. However, there has long been a controversy about how many times the test must be performed to obtain data representative of the individual's functional status, and about which values should be used for analysis of the data. For example, some experts have recommended repeating the test three times; others recommend five repetitions. Some have recommended using the mean value of two or more tests, but others recommend selecting the "best" (i.e., the largest) value.

While these may seem to be technical issues, they are of considerable practical importance in epidemiologic studies that require testing large numbers of subjects and, in prospective studies, that involve sequential measurements in the same individuals over time.

A recently published report, based on data obtained on 3,000 subjects over 3 consecutive years, states that there is no advantage in requiring five tests instead of three, and there is no greater reproducibility when the mean value rather than the largest value is used for data analysis. These observations lend support to the recommendations of the American Thoracic Society for standardized methods to be used in epidemiologic studies (published in 1978). It therefore appears that there is little justification for placing extra demands on the subjects of epidemiologic surveys and for entailing the additional costs involved in repeating spirometric tests more than three times to obtain a reliable value.

Emphysema
—Development of an elastase inhibitor carrier system

Elastin is a structural protein which gives the lung its elastic properties. When excess elastase, the enzyme that degrades elastin, is produced, emphysema may result. Several elastase inhibitors have been synthesized but, when injected into experimental animals, only a small amount reaches the lung. The development of a carrier that would deliver the elastase inhibitor exclusively to the lung would increase effectiveness and decrease side effects, dosage, and frequency of administration. A potentially useful development involves albumin microspheres made by heating human serum albumin in hot vegetable oil. The elastase inhibitor molecules are then attached to the microspheres by molecular chains called spacer side arms. In studies using this size microsphere and chains of a given length, it was found that the microspheres were delivered exclusively to the lungs when injected intravenously and were as effective as native antiprotease in inhibiting elastase. In addition, after 17 days, half of the microspheres were still in the lung. Although this mode of delivery has still not been tested for long-term usage and possible side effects, it does appear to hold considerable promise as a potential therapeutic agent for emphysema.

High-Pressure Nervous Syndrome
—New breathing mixture doubles man's reach under the oceans

It is widely recognized that deep-sea living creates enormous dangers. Divers must live in an underwater chamber in which the atmospheric pressure exactly matches that of the ocean outside. Because oxygen essential for breathing becomes lethal at these extreme pressures, helium is added to reduce the concentration of oxygen. However, pressure forces helium into the divers' bodies so that upon ascent to lower pressures, the helium forms bubbles in the tissues and bloodstream. This results in a painful and sometimes fatal condition known as "the bends." In simulated descents below 1,500 feet, divers have suffered a combination of nausea, shakiness, and fatigue, known as high-pressure nervous syndrome, which severely limits effective work.

This problem has been solved by a new formula of breathable gases consisting of oxygen, helium, and—surprisingly—nitrogen. Breathing this mixture, three volunteer divers recently spent 24 hours working at pressure equivalent to 2,132 feet below sea level, the world's deepest simulated dive. In all, the men spent 27 days in a thick-walled, high-pressure chamber to make the record dive. As cautiously used here, the nitrogen (10 percent) acts as a mild narcotic, reducing the effects of pressure on the brain and nervous system. This achievement suggests that persons can perform useful tasks at depths twice as great as previously thought possible, opening up new worlds of scientific and commercial ocean exploration on the continental slopes some 2,000 feet below the surface.

Cooley's Anemia
—Improvement in methods for treating iron overloads in patients undergoing transfusion therapy

In Cooley's anemia, patients are unable to produce sufficient new red blood cells to replace those that age and die. To provide the patient with adequate red blood cells, transfusions are given. However, this necessary treatment has the side effect of increasing the iron load in the patient's bloodstream. As red blood cells in transfused blood age and die, their iron content accumulates in the patient's blood. To eliminate this iron, various iron chelating agents have been developed.

Currently, the iron-chelating agent desferrioxamine is infused subcutaneously in patients over a period of several hours. An attempt is now being made to improve the method of drug delivery by using red blood cell "ghosts" for the packaging and delivery of iron chelators. Red cell ghosts offer two advantages: reduction of renal loss of the low molecular weight chelators before iron chelation has occurred and potential reduction of the risk of side effects at high dosages (by minimizing exposure of the drug to tissues and organs other than the target sites). Experiments in rats have shown that the total urinary excretion of iron is nine times greater when desferrioxamine is administered in red cell ghosts than when subcutaneous infusion is used.

In related studies, it has been suggested that desferrioxamine has only limited effectiveness because of its inability to remove iron from transferrin, the final common pathway for internal iron exchange. Investigators have postulated that steric hindrance is responsible for this inefficient iron removal and have shown that small molecular weight anions are able to overcome the kinetic barrier *in vitro*. When tested with desferrioxamine *in vivo*, nitriloacetate, citrate, ascorbate, and salicylate were able to induce a two- to threefold increase in urinary iron excretion, as compared to desferrioxamine alone. These anions may have merit as adjuvants to desferrioxamine in the treatment of iron overload.

Cooley's Anemia
—Decreasing transfusion needs of patients with hereditary anemia

Patients with several forms of hereditary anemia require frequent blood transfusions to replace depleted red blood cells. A complication of this treatment is that the red blood cells cannot replace themselves, and transfusions are effective only for the life period of the transfused red cells. In addition, the repeated transfusions allow iron to accumulate in vital organs. These high iron levels are damaging, and iron chelating, or iron extracting, drugs have had to be administered in conjunction with frequent transfusions.

Recently, a new way of managing patients requiring frequent transfusions has been developed. The technique involves extracting the youngest red cells from donor blood. Use of young red cells prolongs the effect of the transfusion and thereby decreases tranfusion frequency and iron accumulation. Recent studies have demonstrated that neocytes (or young cells) survive almost 45 days as opposed to 30 days for ordinary transfused red cells. The central tool in extracting neocytes is a continuous flow cell separation device which is standard equipment in blood banks performing plasmapheresis. Current studies are investigating means to apply this technique to treatment of other red cell disorders, such as sickle cell disease.

Blood Storage
—Improvements may assist sickle cell patients

Currently, red blood cells can be stored for 3 to 5 weeks,* after which they loose viability and become metabolically depleted of 2,3-diphosphoglycerate (2,3-DPG), a molecule that regulates oxygen delivery to the tissues. After 6 years of research, the BAGPM (bicarbonate, adenine, glucose, phosphate, manitol) additive solution has reached the point of final formulation. This preservative solution promises to provide a red blood cell storage medium that will maintain viability and 2,3-DPG levels for 6 weeks. A better understanding of the regulation of 2,3-DPG levels has resulted from these studies and this may provide a means for therapy for sickle cell disease. The effects of this disease stem from the sickling of abnormal red blood cells under conditions of low oxygen tension. It may be possible to increase the oxygen tension of sickled red blood cells in the microcirculation by decreasing the concentration of 2,3-DPG in the red blood cells.

Accidental Poisoning
—Development of detoxifying hemoperfusion device

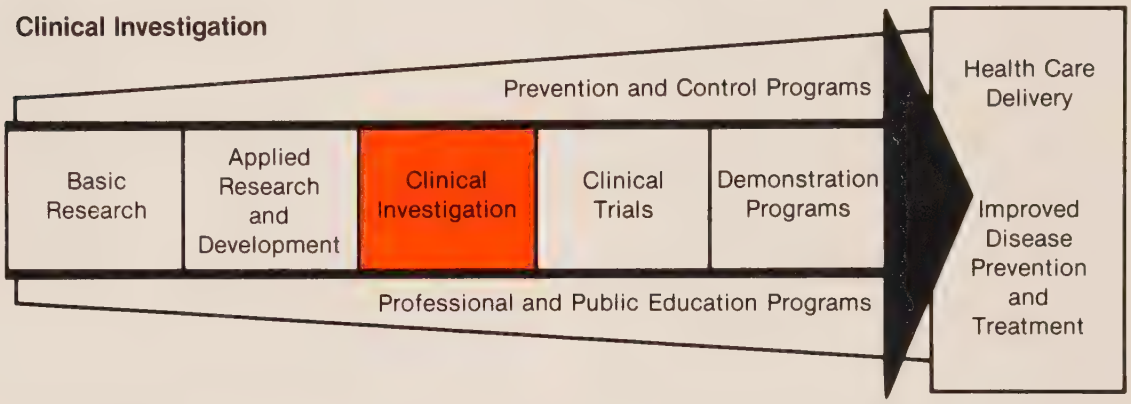
Accidental ingestion of household cleaners, pesticides, and drugs is responsible for thousands of cases of poisoning and death among children every year. Recently, the first activated-carbon hemoperfusion device— a machine clearing the blood of unwanted substances—developed for rescue and life support of young children was produced. This device does not harm the blood cells and, in initial trials in laboratory animals, it has been shown to have an excellent capacity for removing a variety of drugs from the bloodstream. In addition to clearing the blood of a number of commercial poisons, it is thought that this device may also be useful for life support of children with liver or kidney failure and studies are currently being carried out in nonhuman primates in order to mimic similar conditions in children and to test the efficacy of the procedure. Ongoing studies will determine the absorptive capacity of the activated carbon for other substances and it is hoped that application of this technology will significantly reduce the morbidity and mortality associated with accidental poisoning and several childhood diseases.

Nutrition
—Progress in assessment of iron deficiency states

Lack of iron is now recognized as a major deficiency state, affecting 10 to 20 percent of the world population. Reliable methods for assessing the

*At those blood centers that use CPDA (citrate, phosphate, dextrose, and adenine), a recently introduced preservative solution, shelf life has been extended from 21 to 35 days.

iron status of a population are essential for developing effective public health measures to combat iron deficiency. Iron deficiency is usually identified in nutritional surveys by the anemia that accompanies its later stages. However, in certain geographic areas and especially in developing countries, other factors such as folate deficiency, protein-calorie malnutrition, chronic infection, and hemoglobinopathies may cause or enhance anemia. Using the hemoglobin levels as the only measure of iron status accounts for much of the difficulty in evaluating prevalence studies. A model has been developed that uses assays for hemoglobin and other iron transport and storage proteins such as transferrin, free-erythrocyte protoporphyrin, and serum ferritin to evaluate the iron status of a population. This approach may be particularly useful for evaluating the effectiveness of iron supplementation and fortification programs.



Clinical investigation is the vital link between basic and applied research and clinical practice. It provides the mechanisms for translating fundamental research results into potential clinical regimens. Clinical investigations, coupled with basic and applied research, are critical to developing effective therapies to alleviate or delay the effects and progression of disease as well as the design of preventive measures. Further, clinical research translates clinical observations into research focused on determining disease etiology.

Familial Hypercholesterolemia
—Progress toward prevention of atherosclerosis

The recent dramatic increase in ischemic heart disease in developed countries has fostered intense interest in the primary prevention of the condition and, more specifically, interest in methods by which clearance of low density lipoproteins from plasma may be promoted in the prevention of atherosclerosis. Though detailed mechanisms of hypocholesterolemic action are incompletely understood, at least two processes appear to be responsible for LDL clearance in man. The first involves interaction of lipoprotein with specific, high-affinity cell membrane receptors, a process that inhibits autoregulation and that is responsible for approximately one-third of total LDL clearance in normal subjects. The second process involves a receptor-independent mechanism that is not subject to feedback control, or autoregulation, but that clears LDL from a constant fraction of the plasma pool every day. In a recent study, the influence of the drug cholestyramine on these two pathways of LDL catabolism was examined in a group of individuals who were heterozygous for familial hypercholesterolemia. In prior studies, it has been shown that the receptor-mediated LDL clearance rate in these individuals was approximately half that of normal subjects. In this study, cholestyramine administration to these individuals produced a significant increase in the rate of plasma LDL clearance. The data further demonstrated that this increased clearance was due to stimulation of receptor-mediated catabolism, while receptor-independent catabolism was unaffected. These data support the hypothesis that familial hypercholesterolemia results from defective expression of the receptor-mediated LDL clearance mechanism and that, in spite of the genetic defect, affected individuals can increase this activity when presented with an appropriate stimulus.

Coronary Heart Disease
—Prospective study shows decreased risk associated with HDL cholesterol

For the first time in a middle-aged and older population, the inverse relationship between high density lipoprotein cholesterol level in blood and the risk of developing coronary heart disease has been demonstrated in a prospective manner. Previously this relationship had only been inferred from retrospective epidemiological studies, which, while highly suggestive, need to be confirmed by prospective studies.

In the Lipid Research Clinics (LRC) Mortality Followup Study project, 8,825 adults aged 30 to 97, sampled from the 10 North American LRC population surveys, were followed for 4 years after their participation in a lipoprotein quantification study. Analysis was performed on data from men and women randomly selected from a group of 7,180 white adults who were clinically free of ischemic heart disease at their initial survey. After controlling for known risk factors such as blood pressure, smoking, and obesity, preliminary results showed that HDL cholesterol was negatively related to total mortality in females and to fatal ischemic heart disease in males. For males, plasma cholesterol was positively related to ischemic heart disease deaths, positively but not significantly related to cardiovascular disease deaths, and negatively but not significantly related to noncardiovascular disease deaths. Adjustments for length of followup did not alter the results. Although not final, findings from this study tend to confirm previous epidemiological observations and emphasize the need for additional research on the relationship between HDL cholesterol and coronary heart disease.

Coronary Heart Disease
—Protective effect of complex carbohydrates

In the past, various studies have implied that there is a direct relationship between dietary patterns and habits and the risk of developing coronary heart disease. To more fully investigate this relationship and to ascertain which dietary patterns, if any, conferred protection against this risk, a 6-year study of the nutritional intakes and habits of middle-aged urban and rural Puerto Rican men was undertaken. Overall the study showed that urban men had a higher incidence of myocardial infarction and coronary heart disease death than their counterparts in rural areas. Furthermore, the dietary intake of urban men was found to be significantly higher in total fat and cholesterol and lower in total calories and carbohydrates, especially starches derived from rice and legumes. Dietary sucrose, however, was unrelated to the incidence of coronary heart disease. Analysis of data obtained in this study, taking into account other coronary heart disease risk factors such as weight, blood pressure, alcohol intake, and smoking, demonstrated an independent inverse relationship between carbohydrate intake from legumes and the incidence of coronary heart disease. Intake of complex carbohydrates from legumes appears to offer a protection effect against the risk of developing coronary heart disease, independent of other risk factors, and merits further investigation.

Coronary Heart Disease
—Psychological factors and heart disease in women

Lifestyles, particularly working habits, have changed dramatically for women in recent years. In addition to the standard coronary risk factors, as more and more women enter the work force they are becoming exposed to employment-related behaviors which may be related to the increased risk of developing coronary heart disease. Over a 10-year period, the employment status and employment-related behaviors of a group of homemakers and working women were examined in relation to the incidence of coronary heart disease. Despite several behavioral differences between women employed inside and outside the home, working women did not have significantly higher rates of coronary heart disease than homemakers. Coronary heart disease rates were twice as great, however, among women holding clerical jobs as among those in professional positions. The most significant predictors of coronary heart disease in clerical workers were suppressed hostility, having a nonsupportive boss, and decreased job mobility. On the whole, coronary heart disease rates were also higher in working women who had married and raised three or more children. It was found that those working women at the highest risk for developing coronary heart disease were clerical workers who had children and who were married to blue collar workers. This study suggests that interpersonal relationships, coping styles, and the occupations of some women, coupled with family responsibilities, may be involved in the development of coronary heart disease.

Coronary Heart Disease
—Family history as potential predictor of myocardial infarction

The incidence of various forms of coronary heart disease has been associated with numerous risk factors such as hypertension, elevated serum cholesterol, and cigarette smoking. The relationship of various risk factors to the incidence of clinically recognized coronary heart disease was studied in spouse and sibling pairs in the Framingham Heart Study cohort. Among spouse pairs, no aggregation of coronary heart disease was found but certain coronary heart disease events showed significant aggregation in sibling pairs. For example, the incidence of myocardial infarction (MI) in the older siblings of the pairs was significantly related to MI experience in the younger siblings even after the strong effects of total serum cholesterol, systemic blood pressure, and cigarette smoking were controlled. These findings suggest that family history of MI may be an important predictor of subsequent MI in other family members and suggest that familial aggregation of coronary heart disease may result from a genetic predisposition to disease that is not related to other measurable risk factors.

Coronary Heart Disease
—New techniques of patient evaluation

One of the central problems in treating myocardial infarction is identifying those patients who have a high risk of repeated heart attacks or the probability of consequent mortality. If patients who are at

high risk can be properly identified, rigorous treatment can be initiated to prevent further complications.

Recent studies have examined the hypothesis that response to exercise may prove a reliable indicator of mortality in the year following myocardial infarction. One study has shown that a limited treadmill exercise test performed 1 day prior to hospital discharge can be used to predict mortality in the subsequent year for selected patients who have had a myocardial infarction. Depression of the S-T segment during the test, with or without angina, was highly predictive of mortality in the subsequent year. Although only 30 percent of the patients had this abnormality, 91 percent of sudden deaths and 85 percent of all deaths occurred among patients with the abnormality. The test is expected to be of major value in helping physicians determine which patients require most aggressive therapy routines and in whom the side effects and inconvenience of therapy may be most worth accepting.

Coronary Artery Disease

—Coronary artery bypass effects on regional and left ventricular function evaluated

Coronary artery bypass surgery is an important treatment for coronary heart disease. In this operation, blocked blood vessels are bypassed by grafting new sections of blood vessel onto the vasculature of the heart. However, coronary revascularization does not consistently improve left ventricular function when patients are evaluated at rest. This finding is important because it implies that rest abnormalities of function may be irreversible, while it may still be possible to reverse abnormalities induced by exercise if revascularization can improve myocardial perfusion.

Recent studies have evaluated the effect of revascularization on left ventricular function in patients during exercise. At rest, ejection fraction was unchanged after surgery, but 17 of 23 patients demonstrated improvement in ejection fraction during exercise. All patients with improved ejected fraction were symptomatically improved. The investigators conclude that, while coronary revascularization has little effect on left ventricular function at rest, ejection fraction during exercise and exercise induced with motion abnormalities are improved. The amelioration of symptoms by coronary revascularization is usually due to augmentation of functionally important myocardial perfusion.

Angina Pectoris

—Coronary artery spasm shown to cause angina, arrhythmias, and even infarct

For a long time scientists have thought that angina pectoris, arrhythmias, and cardiac tissue damage are caused by fixed blockage of the blood vessels supplying the heart. Many therapies such as coronary artery bypass and diet control are based on this concept. However, recent studies have suggested additional causes of such disorders. It has been shown that in some patients spasms of the coronary arteries can also obstruct coronary blood flow, thus causing angina, arrhythmia, or infarct. While these findings do not controvert evidence of the causal role of fixed blockage, they do suggest that other factors, which cannot be surgically controlled, must also be considered. Recent studies have shown that calcium antagonists such as nifedipine, verapamil, perhexilene, and diltiazen can control vasospasm. They often eliminate angina attacks and appear to reduce the risk of myocardial infarct.

Heart Surgery

—New techniques for preventing postoperative heart damage

Despite major advances in cardiac surgery, some operations still result in early postoperative death. Most often the death is caused by some form of acute heart failure, which is usually related to new and often extensive myocardial necrosis (or tissue damage). Recent research has developed new techniques of myocardial protection to reduce the occurrence and extent of perioperative myocardial necrosis.

Several techniques to limit necrosis have been developed. All have certain limitations, however. Recently the technique of cold cardioplegia (cooling of the heart and induction of electromechanical arrest) has shown considerable promise. By this method the temperature of the heart is lowered during the period when blood supply to the heart is diminished and the electromechanical activity of the heart is terminated at the onset of ischemia. This technique reduces oxygen consumption to such low levels that the energy stores in the heart tissue are sufficient to maintain cellular structure. Although cardioplegia has clearly improved the early results of cardiac operations, the long-term effects of the procedure have not been determined. Several details of the technique are also yet to be defined. Among these are determination of the best solution concentration of the arresting agent, the benefits of adding agents to the solution to protect the heart tissue, and the best temperature at which to maintain the myocardium during the ischemic period. Nonetheless, cold cardioplegia promises to dramatically improve the early and late results of cardiac operations and to allow more extensive and precise operating procedures.

Cardiac Arrhythmias

—New mapping technique improves treatment

Recurrent ventricular tachycardia is sometimes associated with ventricular aneurysms following myocardial infarction. In some cases of ventricular tachycardia that have proved to be refractory to medical therapy, it has also been found that aneurysmectomy alone may not be consistently effective in abolishing this dangerous arrhythmia.

Therefore, the technique of endocardial and epicardial mapping has been used in a group of patients to examine the transmission of electrical impulses in the diseased area of the heart and to identify the probable site where the arrhythmia is originating in the endocardial tissue prior to surgery.

In a recent study, complete resection of the arrhythmic site was possible at surgery in a majority of cases, with partial resection accomplished in the remainder. In those patients undergoing total resection, no ventricular tachycardia has recurred during the followup period and those patients with partial resections are being successfully controlled with antiarrhythmic drugs. Thus the prognosis for patients undergoing surgical correction of recurrent ventricular tachycardia associated with aneurysm has been greatly improved through identification of the endocardial origin of the arrhythmia followed by appropriately guided resection.

Congestive Heart Failure
—New uses for captopril in treating congestive heart failure

Captopril is a new oral drug that lowers blood pressure by blocking production of a potent vasoconstrictor, angiotensin II. Recently, new applications of captopril have been reported in the treatment of congestive heart failure. Patients who have experienced heart failure and have been maintained on captopril have been followed over a period of a few months. The patients are showing sustained clinical improvement, including increased exercise tolerance and reduction in heart size. Apparently, captopril lowers systemic vascular resistance while improving cardiac output. It has been suggested that captopril has this effect because some heart failure patients have vasoconstriction caused by increased renin-angiotensin and plasma-renin activity. Further study will be needed to determine the exact mechanisms by which captopril improves the prognosis for heart failure patients.

Congestive Heart Failure
—Promising new drug for refractory cases

Cardiotonic agents are used in patients with congestive heart failure to increase the state of partial contraction characteristic of normal muscle tissue. The acute effects of one such newly synthesized drug, an oral preparation of amrinone, were recently assessed by noninvasive means in nine patients who had advanced heart failure that persisted despite treatment with digitalis, diuretic drugs, and afterload-reducing agents. All patients demonstrated an improvement in left ventricular ejection fraction determined by radionuclide ventriculography after a single dose of amrinone. Initial effects were seen within 1 hour, with the peak effect occurring at 1 to 3 hours; persistent effects were demonstrable at 4 to 6 hours. No change in blood pressure, heart rate, or rhythm was observed, and there was no clinical evidence of myocardial ischemia. Continued benefit was demonstrated by radionuclide ventriculography in two patients treated for 1 and 6 weeks, respectively, although two other patients experienced major side effects with the chronic administration of amrinone. Although orally administered amrinone shows promise as a potentially useful agent in the treatment of advanced heart failure, the safety of this drug remains to be established.

Acute Heart Failure
—Vasodilator produces sustained hemodynamic improvement

Acute heart failure severely affects the ability of the heart to pump adequate supplies of blood. Various drugs have been developed to improve the heart's ability to recover its hemodynamic functions. In recent studies, hydralazine (a vasodilator) has been shown to produce sustained hemodynamic improvement. After 20 mg of hydralazine was given intravenously over a 10-minute period, increases of 56 percent in stroke volume index and 64 percent in cardiac index were associated with a decrease of 27 percent in pulmonary arterial diastolic pressure. Mean arterial blood pressure decreased 16 percent but heart rate was not significantly changed. Seven patients who completed 4 to 6 weeks of treatment with oral hydralazine showed sustained hemodynamic improvement. The cardiac index increased 7 percent and the stroke volume index 71 percent, while the pulmonary arterial diastolic pressure decreased 25 percent. It would appear that few drugs are as capable of producing such substantial sustained increases in cardiac output as is hydralazine. However, whether these increases are maintained with exercise has not yet been determined.

Chronic Obstructive Lung Disease
—Is alcohol consumption a risk factor?

It has long been known that alcoholics are at increased risk of chronic obstructive lung disease as well as tuberculosis, pneumonias, lung abscesses, and lung cancer. It is not known, however, whether this is a consequence of alcohol consumption per se, or is related to risk factors such as the lifestyle of alcoholics or greater frequency of smoking in this group. It is also not known whether alcohol consumption is a risk factor for chronic obstructive lung disease in the general population.

To answer these questions, 2,539 adults who are being followed in an epidemiology project were examined for their drinking habits as well as other risk factors. The ratio of forced expiratory volume in 1 second to forced vital capacity (FVC) was used as an indicator of airway obstruction in comparing light, moderate, and heavy drinkers.

Although heavy drinkers appeared to have diminished pulmonary function, when the figures for FEV_1/FVC were corrected for such relevant variables as smoking, sex, age, socioeconomic status,

etc., the difference between heavy drinkers, moderate drinkers, and light drinkers disappeared. The investigators concluded that, for the general population, risk of airway obstruction cannot be attributed directly to the amount of alcohol consumed.

Emphysema and Chronic Bronchitis
—Is cigarette smoke in the environment a hazard to nonsmokers?

Despite vigorous debate about public policies to shield nonsmokers from exposure to cigarette smoke, there are few hard data to support the view that "passive smokers" are at increased risk of such chronic lung disorders as emphysema and chronic bronchitis. A recent study widely reported in the national press provides the first quantified evidence that nonsmokers exposed for 20 or more years to smoke from cigarette smokers in their workplace have a small, but statistically significant, diminution in function of the small airways. This evidence of a physiologic change in nonsmokers who inhale cigarette smoke from the environment does not, however, answer the question of whether such individuals are at greater risk of chronic diseases of the airways.

Another study addressing this issue examined the children of smoking parents and obtained evidence that the symptom of wheezing in children aged 5 to 10 years is associated significantly with the level of parental cigarette smoking. This effect occurs not only in children diagnosed as having asthma but also in those who wheeze but have never had a diagnosis of asthma. Moreover, the symptom of wheezing, even in the absence of a diagnosis of asthma, is associated with lower levels of pulmonary function in these children. Further study is necessary before it can be determined whether these children are at a greater risk of chronic airway obstruction in later life.

Asthma
—Behaviors that interfere with successful medical management

It is well known that patients with asthma vary widely in their responses to standard, accepted modes of therapy, and that some of these differences are a consequence of physiologic differences in responsiveness of the airways. In other instances, confounding factors in the treatment of patients with asthma are behavior patterns that lead to noncompliance with medical regimens, or to an inability to cope with the effects of the disease.

A study in progress for some years has now advanced to the point of developing a "battery of asthma illness behavior" that enables the investigators to identify personal styles or behavior patterns that can defeat medical management. The battery provides the basis for predicting whether a given patient is likely to use antiasthma medications in ways that are potentially dangerous to himself, misleading to his physician, and a threat to his medical management. It can also be used to predict the likelihood of continued high rates of hospitalization because of the patient's personal style.

These maladaptive personal styles affect not only the patient but also the cost of care. It has been estimated that for 181 patients over a 2-year period, about $285,000 of medical expenditures for hospitalization costs were incurred that were in excess of what was to be expected for the actual severity of the asthma.

Asthma and Chronic Bronchitis-Emphysema
—Interrelationship revealed in epidemiologic studies

Several recent studies point to a relationship between the hyperreactivity of airways that characterizes asthma and other chronic lung disorders. In an epidemiologic study to determine the relative importance of different risk factors for development of airways obstruction, hyperreactivity of the airways (determined by methacholine challenge) was found to be more frequent in sons of patients with chronic obstructive pulmonary diseases than in sons of a control group without this respiratory disorder. These observations suggest that a familial component of airway obstruction is related to airway hypersensitivity, and that a test of this reactivity may provide a sensitive index of risk for developing chronic obstructive lung disease. These results are consistent with others from a natural history study of airways obstruction in nonsmokers in a rural population minimally exposed to air pollution. In this group, a history of asthma was significantly associated with progressive ventilatory deterioration and with mortality. An association has also been found between a family history of asthma and bronchopulmonary dysplasia in 17 members of a group of 39 infants who survived neonatal respiratory distress syndrome. A history of physician-diagnosed asthma was found in family members of 75 percent of the infants with bronchopulmonary dysplasia, compared with such a history in 33 percent of the other 21 infants. A family history of hospitalization for asthma was found in 59 percent of infants with bronchopulmonary dysplasia, but in only 14 percent of those who did not develop the chronic lung disorder.

Exercise-Induced Asthma
—Relationship to cooling of the airway

The well-recognized phenomenon of exercise-induced bronchospasm experienced by asthmatic subjects has been variously attributed to such diverse factors as mechanical stimulation of the tracheobronchial tree that results from high minute ventilation during exercise; lowering of alveolar carbon dioxide tension; or release of humoral agents by exercising muscles. However, a recent series of studies has led to the hypothesis that the initiating stimulus to bronchospasm in exercise-induced asthma is a loss of heat by the mucosal lining of the

airway. Investigation of this phenomenon stemmed from the observation that many asthmatic subjects experienced more severe airway obstruction when exercised in a cold environment. Subsequent studies established that cold alone will induce airway obstruction in asthmatics, and that there is a positive correlation between the total heat loss from the airways during exercise and the severity of obstruction. The greater constrictive response associated with greater heat loss is attributed to the large volume of air that reaches the airways during exercise before the air has been thermally conditioned. This results in cooling of the airway mucosa as heat is transferred from the airway lining into the cooler air. The investigators believe that this respiratory heat loss is the initiating stimulus to the airway obstruction that asthmatic subjects experience after exercise. Since normal subjects also experience bronchoconstriction upon exposure to cold, but are much less sensitive than asthmatic subjects, the investigators are now endeavoring to determine the basis of this difference and the mechanisms involved in the alterations in the airways that occur in patients with asthma when the airways are cooled.

Sudden Infant Death Syndrome
—Evidence for a familial tendency in defective ventilatory control

Sudden infant death syndrome (SIDS), which accounts for approximately 10,000 deaths each year in seemingly healthy infants between the ages of 1 month and 1 year, is still poorly understood. Although there have been numerous hypotheses, data collected over the past 10 years suggest that defective mechanisms of respiratory control may be a key factor in this syndrome.

Previous studies comparing identical and nonidentical twins, offspring of hypoventilating and nonhypoventilating patients with chronic obstructive lung disease, and of nonathletic parents or siblings of successful endurance athletes who have decreased ventilatory drive, all point to the existence of familial tendencies or genetic determinants of ventilatory drive. These observations stimulated interest in whether there is also a familial tendency to abnormalities of ventilatory control in sudden infant death syndrome, a possibility suggested by some evidence that there may be familial clustering in sudden infant death syndrome as well as in "near misses," in which infants found to be apneic were resuscitated.

In a recent study, the ventilatory responsiveness to carbon dioxide was measured in a group of 12 parents (6 couples) of victims of sudden infant death syndrome and a control group of 12 parents (6 couples) with no family history of this syndrome. The control group was matched with the test group for age, body size, and sex. Ventilatory response and respiratory drive were measured both with and without added resistance to inspiratory flow. SIDS parents had significantly lower ventilatory responses (i.e., less of an increase in ventilation with increasing levels of inspired carbon dioxide) with added resistance and without it, and significantly lower respiratory drive with and without added resistance. Control parents had significantly increased respiratory drive when the resistance was added, whereas SIDS parents did not.

These observations suggest that persons who exhibit low ventilatory responses to carbon dioxide and low responsiveness to increased airway resistance may be at increased risk of having children who are susceptible to sudden infant death syndrome.

Hyaline Membrane Disease
—Artificial surfactant therapy developed

Hyaline membrane disease is a lung disorder found in premature infants. The underlying process is thought to be a deficiency of alveolar surfactant that results in progressive neonatal atelactasis. An obvious therapy is to administer surfactant through the airways. To date, animal studies have shown that only natural as opposed to synthetic surfactant has proved effective; however, natural surfactant cannot be used in humans.

Recently, Japanese investigators have developed an artificial surfactant that closely resembles pulmonary surfactant. It consists of a mixture of naturally occurring and synthetic lipids containing dipalmitoye lecithin and phosphatidyl glycerol. The therapy has been tested in 10 infants severely ill with hyaline membrane disease. Radiological appearance of the lungs, arterial oxygenation, acid-base balance, and alveolar-arterial oxygen tension gradient all improved rapidly and the infants needed less oxygen and less ventilation pressure. A single dose of artificial surfactant seemed effective throughout the course of hyaline membrane disease. The investigators believe their findings are sufficiently encouraging to justify further trials.

Severe New Pulmonary Syndrome
—Practical and theoretical implications

A recent report of a new pulmonary syndrome that results from exposure to trimellitic anhydride is of considerable practical interest because this substance is widely used in the manufacture of plastics. Workers are exposed to trimellitic anhydride dust during its manufacture, or to its fumes when a plastic spray containing the substance is used to coat pipes heated to several hundred degrees. Because trimellitic anhydride is a simple chemical compound, there is also considerable theoretical interest in its effects, which appear to be immunologically mediated and to be similar to immune responses usually associated with inhalation of more complex organic dusts.

The most recent finding of a new pulmonary syndrome emerged from a study of exposed workers that had been in progress for a few years, a study

that previously identified three different clinical entities resulting from trimellitic anhydride exposure. One is an immediate irritant response that results from exposure to trimellitic acid, a highly acidic hydrolysis product of trimellitic anhydride. The other two clinical entities correlate with specific immunologic responses to the anhydride. One is a respiratory response characteristic of asthma and involving IgE antibodies. The other, a flu-like syndrome resembling hypersensitivity pneumonitis, involves IgG antibodies. The fourth, recently observed, syndrome is characterized by anemia as well as pulmonary symptoms that include cough, blood in the sputum, shortness of breath, and evidence of pulmonary infiltrates in the chest X-ray. This syndrome varies in severity from mild to life-threatening and in severe cases requires ventilatory support.

Studies are in progress to determine the immunologic characteristics of exposed workers who develop this "pulmonary disease-anemia syndrome," of similarly exposed workers who are asymptomatic, and to determine the relevance of such findings to the possible immunopathogenesis of this trimellitic anhydride-induced syndrome.

Pigeon Breeders Disease

—Differences in cellular immunity

Pigeon breeders disease, a form of hypersensitivity lung disease (pneumonitis) that results from exposure to pigeon droppings, is associated with the presence of antibodies specific to pigeon antigens. These antibodies are present in all persons with the disease, but are also found in more than half of pigeon breeders who are free of the disease. There is also a marked difference in the course of disease: some breeders with the disease maintain a stable course in spite of continued exposure to pigeon antigen, while others show progressive deterioration over the years. A recent study has now shown that a test of cellular immunity can discriminate between sick breeders and those who are well. In this test lung lymphocytes obtained by lavage are examined to determine whether they take up thymidine when stimulated by pigeon antigen. Only the lymphocytes of sick breeders show this reaction. It is also of interest that pulmonary function tests may help identify individuals with pigeon breeders disease who are likely to have a downhill course. In a long-term followup study of ill pigeon breeders, those whose pulmonary functions were normal on initial study maintained a stable course in spite of continued exposure to pigeon antigen. On the other hand, breeders with abnormal initial pulmonary functions tended to deteriorate over the years.

Sarcoidosis

—Increase of specific enzyme may help in diagnosis

Sarcoidosis is a granulomatous disease that affects many organs in the body, including the lungs. Although the disease was first described 100 years ago, the cause remains unknown. Diagnosis typically requires the tedious exclusion of other diseases. Biopsies of lymph nodes, lung tissue, liver, and skin are often required to make a diagnosis of sarcoidosis and to exclude the presence of other diseases such as tuberculosis, fungal infection, or beryllium disease. About two-thirds of the patients diagnosed as having sarcoidosis recover spontaneously within a year or two of the time that the diagnosis is made. The remaining one-third have a chronic form of disease and are often treated with corticosteroids in an attempt to ameliorate symptoms, to improve lung function, and to prevent damage to the lung and other organs.

In a search to identify an *in vitro* method to detect sarcoidosis, several investigators have been studying the significance of the increase in the level of a specific enzyme, angiotensin converting enzyme, in the serum of patients with this disease. Using a sensitive spectrophotometric assay to detect converting enzyme activity, one study found increased levels of this enzyme in 79 percent of the 42 sarcoid patients examined, compared to only 5 percent of normal adults. It appears that the serum level correlates with extent and severity of disease. Of further interest is the decrease in enzyme activity when the subjects undergo conventional therapy and the recent report of a fivefold increase in enzyme activity in alveolar macrophages from patients with sarcoidosis compared to subjects without the disease.

Longitudinal studies must still be undertaken before increases in serum angiotensin converting enzyme can be confirmed as useful for diagnosing sarcoidosis, and further studies are required to understand the role of the alveolar macrophage in the synthesis and secretion of the enzyme. However, the ability to correlate serum levels of angiotensin converting enzyme with the presence of active sarcoidosis and to identify an increase in enzyme activity in a specific lung cell type appears to be a promising step in unraveling the enigma of this disease.

Chlorine Gas Exposure

—Followup study of survivors

Epidemiologists have long deplored the loss of data of great potential value because neither resources nor personnel can be readily mobilized to study the health impact of sudden natural or industrial disasters that affect sizable populations. For this reason it is of special interest that a group of investigators involved in studies of various environmental diseases were able to mobilize their resources rapidly enough to undertake a followup study of the long-term effects of high levels of exposure to chlorine gas that was released in a freight train derailment. Within 3 weeks of the derailment, which occurred in February 1978, in Youngstown, Florida, the investigators were able to initiate a field study

of approximately 100 survivors of heavy exposure to the gas. The accident resulted in 8 deaths, and 147 survivors sought treatment for the exposure. Of these, 26 were hospitalized.

Although the acute effects of chlorine exposure are known to be severe and can include pulmonary edema and pneumonia as well as the inflammatory responses of the airways, this study is addressing the extent of permanent residual effects on the respiratory system in survivors of the exposure. After the first year of followup, it has been demonstrated that smokers have a significantly less favorable longitudinal course in ventilatory function than do nonsmokers, and that this smoking effect is most noticeable during the first 6 months after exposure. Later studies will answer the question of whether such differences in ventilatory function persist long after the exposure.

Respiratory Disease
—Immunologic factors in individual responsiveness to environmental hazards

A challenging question is why some individuals exposed to environmental hazards develop respiratory diseases, while others similarly exposed remain free of disease. Among many host factors believed to modify susceptibility to a given respiratory disease, the immunologic characteristics of individuals are being examined to determine whether they are associated with increased or decreased risk.

More than 50 human lymphocyte antigens (HLA) have been identified, and numerous investigations have been undertaken to determine whether any of these are associated with occurrence of a particular respiratory disease. Among the diseases already studied and found not to be associated with any of the HLA types are sarcoidosis, cystic fibrosis, asthma, and pigeon breeders disease (a form of hypersensitivity pneumonitis). It is therefore of considerable interest that study of individuals exposed to asbestos dust has shown that persons with a particular antigen (HLA-B27) are 2-1/2 times as likely to develop asbestosis as matched controls who were similarly exposed but lack this antigen. On the other hand, there is also some evidence that an HLA type may confer resistance. Two types (HLA-BW21 and HLA-A1) appear to be associated with resistance to coal workers pneumoconiosis. One of these (HLA-A1) is associated with resistance to development of both simple and complicated forms of this disease, while the other (HLA-BW21) is associated with resistance to development of progressive massive fibrosis.

Respiratory Failure
—Coping with respiratory disorders

There is mounting awareness of the importance of adequate nutrition to the maintenance of normal function of muscles that are essential to normal breathing. They include the diaphragm, muscles between the ribs, and others that are part of the chest wall. When they contract, pressure in the pleural spaces that surround the lung is lowered, the lung inflates, and air from the environment enters the lung (inhalation).

Recent investigations of the functional capacity of the respiratory muscles when nutrition is impaired were stimulated by the observation that patients who had lost a great deal of weight prior to death had wasted diaphragms. It has now been found that, in patients with various lung diseases, inadequate nutrition compromises the ability of the respiratory muscles to cope with the respiratory disorder. Moreover, even in patients who have no disease of the lung or chest wall, but who have severe nutritional disturbances due to disease elsewhere in the body, the strength and endurance of their respiratory muscles were less than one-half normal and the patients manifested comparable reductions in their performance on routine breathing tests.

These are important observations because when breathing impairment is sufficiently severe it may result in acute respiratory failure—a frequently fatal syndrome. These acute consequences may occur in disorders that increase the work of breathing. In obstructive diseases of the airways, such as emphysema and chronic bronchitis, breathing is more difficult because of high resistance to airflow in the bronchial air passages. In fibrotic lung diseases, such as coal workers pneumonconiosis or asbestosis, breathing is impaired owing to stiffening of the lung, and, in some systemic connective tissue diseases, stiffening of the chest wall may increase the work of breathing. In all of these conditions, nutritional impairment will contribute to the patient's difficulty in coping with the respiratory disorder.

Smoking and Fetal Development
—Effects on oxygen affinity

Despite the dogma that the fetus derives oxygen from the mother by virtue of the fetus's having a higher oxygen affinity hemoglobin, successful pregnancies have been observed in humans with hemoglobin oxygen affinities as high as P_{50}=12 mm Hg. In such a case, the hemoglobin of the mother actually has a higher oxygen affinity than that of the fetus and this should greatly impede oxygen transport to the fetus. The effects of abnormally increased maternal hemoglobin oxygen affinity have been examined in rats in an attempt to define what, if any, detrimental effects it might have on fetal well-being. Conversely, such studies provide insight into the protective efficacy of high fetal-hemoglobin oxygen affinity. Results indicate that when fetal and maternal oxygen affinities are equal from the ninth day of gestation (term is 22 days), fetal weight is 10 percent lower at term and this is accomplished by placental hypertrophy. The rather small decrement in fetal weight in these rats indicates that the high oxygen affinity of mammalian fetuses is, indeed, a very efficacious mechanism for protecting

the fetus against hypoxia. It is interesting that the decrement in weight of newborns is of the same magnitude as the weight deficit in newborn offspring of human mothers who smoke. However, the perturbation of maternal oxygen transport in the case of mothers who smoke is much smaller than in the above experiments. This suggests that the adverse effects of maternal smoking on the newborn are not due solely to the effects of carbon monoxide on the maternal oxygen transport (decrement in oxygen-carrying capacity and increased oxygen affinity).

High Altitude
—Is decreased oxygen affinity maladaptive?

Decreased oxygen affinity of hemoglobin seen in humans at high altitudes (newcomers and permanent residents) is believed to be of adaptive value, for such a decrease in hemoglobin oxygen affinity would appear to facilitate oxygen delivery at the tissue level. However, this decrease in oxygen affinity at high altitude might actually be maladaptive, since it would worsen the major physiologic stress of altitude exposure, decreased arterial oxygen saturation.

To test this hypothesis, studies were performed on two adolescents heterozygous for hemoglobin Andrew-Minneapolis and two normal age- and sex-matched siblings at an altitude of 3,100 meters. The oxygen affinity of the children with Hb Andrew-Minneapolis was such that their arterial oxygen saturation was maintained at 97 percent, whereas that of the control subjects dropped to less than 90 percent. Therefore, the subjects with high oxygen affinity were almost unaffected by altitude-induced arterial desaturation. The physical performance of individuals with high oxygen affinity, though somewhat below normal at low altitude, was unaffected at 3,100 meters. In contrast, that of the control subjects was decreased by 23 percent. Similarly, brisk increment in resting heart rate was observed in the normal subjects at 3,100 meters, whereas the children with high oxygen affinity showed little increase. For a given exercise workload, normal subjects manifested greater heart rates at high altitude, whereas subjects with high oxygen affinity showed almost no change. These results indicate that increased, rather than decreased, hemoglobin oxygen affinity is of adaptive value at high altitude.

Mountain Sickness
—A drug to improve blood oxygen levels during sleep at high altitudes

During sleep, blood oxygen saturation may decrease dramatically in normal healthy individuals who go to high altitudes. This phenomenon is of concern with the increase in the number of individuals who undertake mountain climbing as a recreational activity. A diuretic drug, acetazolamide, was given to nine healthy mountaineers in a high altitude laboratory on Mount Logan in the Yukon Territory. The drug lessened symptoms of acute mountain sickness such as insomnia, periodic breathing, and morning headache. By close monitoring of the subjects, it was shown that the beneficial effect of the drug resulted from increased ventilation and hence improved arterial oxygen saturation during the sleep period. The drug appeared to work in all stages of sleep; all subjects reported that they slept well.

Hepatitis
—Screening blood donors for non-A, non-B hepatitis

Viral hepatitis is still a significant posttransfusion complication. Despite the routine screening of donor blood for hepatitis B, posttransfusion hepatitis can be detected in approximately 7 to 10 percent of blood recipients. Non-A, non-B hepatitis accounts for 90 percent of those cases. The reality of non-A, non-B hepatitis is now firmly established in an epidemiological and clinical sense; however, little is known about the causative agents. Therefore, serologic screening of donor blood, which has proved so effective for the control of hepatitis B, will have to await identification of the responsible agent or agents.

A recent collaborative study has shown that donor blood containing elevated levels of alanine aminotransferase (ALT) carries a high risk of infectivity for non-A, non-B hepatitis. ALT is an enzyme present in high quantities in the liver. Similar to the way injured muscles release creatine phosphokinase and signal heart muscle injury, an inflamed or infected liver may release large quantities of ALT into the bloodstream. Screening donor blood samples for ALT may be useful as an interim assay for reducing the incidence of posttransfusion hepatitis.

Sickle Cell Disease
—False positive results in lead screening

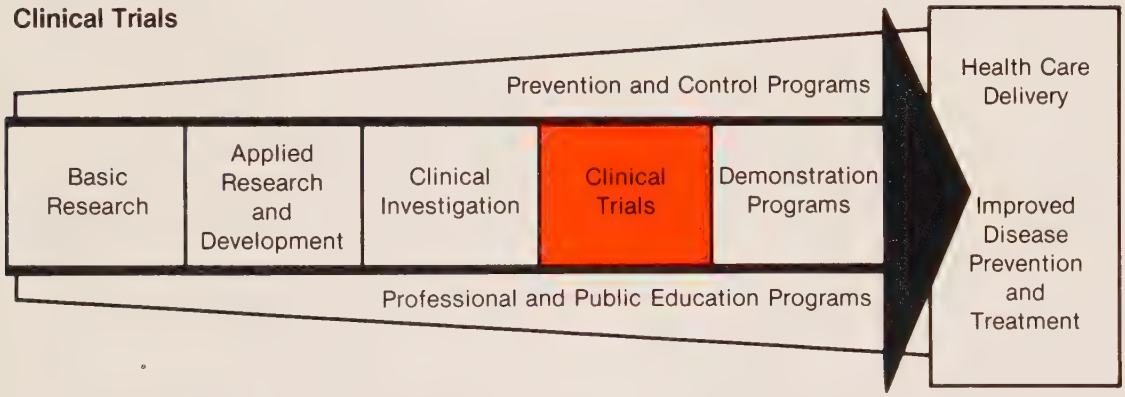
Although blood tests for lead concentration and erythrocyte protoporphyrin are accepted screening methods for increased lead absorption among hematologically normal children, no systematic evaluation has been made of their use in children with sickle cell disease. A group of children with sickle cell anemia who were asymptomatic for signs of lead poisoning have been studied, and the erythrocyte protoporphyrin levels were elevated in approximately half of the group. It has been observed that protoporphyrin is frequently elevated in children with sickle cell anemia in the absence of iron deficiency and increased lead burden. This result can probably be explained by the fact that the laboratory method used measures total erythrocyte protoporphyrin. In lead poisoning and iron deficiencies, zinc protoporphyrin is elevated, whereas

immature erythrocytes contain increased levels of protoporphyrin IX. It has been shown that this "free" molecule accounts for 50 percent of the total erythrocyte protoporphyrin in patients who have sickle cell anemia. Thus, the use of erythrocyte protoporphyrin concentration in screening for lead poisoning in patients with sickle cell disease leads to an unacceptably high ratio of false positive results. Diagnosis of true lead poisoning in such children would appear to require the use of EDTA (edetate) mobilization tests in those suspected of having significant increased lead burden.

Cooley's Anemia
—Safer methods of prenatal diagnosis

During the past 5 years fetoscopy has been used as a means of prenatal diagnosis of the major hemoglobinopathies, thalassemias and sickle cell anemia. The results have been promising, but the procedures for fetal blood sampling are invasive and require a high degree of obstetric skill. It would be desirable to approach such diagnoses by the use of fetal fibroblasts, when possible, because the acquisition of these cells from amniotic fluid is both safe and reliable. Investigators have recently developed a more direct technique to diagnose thalassemia syndromes. The method allows the assessment of the globin genes present in total cellular DNA and is applicable to amniotic-fluid cell DNA. Cellular DNA fragments produced by cleavage using two specific restriction endonucleases (enzymes that cleave the DNA molecule) are separated on the basis of size by agarose-gel electrophoresis, and the distribution of specific sequences among the DNA fragments is determined by molecular hybridization. The total deletion of alphaglobin genes in homozygous alpha-thalassemia (hydrops fetalis with hemoglobin Bart's) and the depletion of particular beta and beta-like sequences in cases homozygous for hereditary persistence of fetal hemoglobin and delta, beta-thalassemia was observed. Analysis of amniotic fluid cell DNA from a fetus at risk for delta, beta-thalassemia demonstrated the feasibility of these improved methods for prenatal diagnosis. The molecular studies confirmed the diagnosis predicted by analysis of fetal blood and established at birth.

Clinical Trials



Clinical trials test, in a carefully controlled setting, the efficacy and safety of preventive and therapeutic regimens with the potential to save hundreds of thousands of lives and billions of dollars each year. The clinical trial is a key step in the long, difficult, and complex process which converts research findings to clinically applicable prevention or treatment regimens.

The objective of the large-scale clinical trial—a critical activity in the biomedical research spectrum—is to gain information regarding the effect of a given form of medical or surgical intervention. Clinical trials are used to test new drugs, compare alternative patient management modes, determine the effectiveness of different treatments, or measure the efficacy of intervention programs for high-risk populations. Trial results validate the projection of potential consequences of successful intervention—risk reductions, changes in longevity, morbidity, and mortality, and economic savings.

The conduct of a clinical trial involves a series of steps, each with its own stringent requirements. Consequently, the time needed to successfully complete a trial can range anywhere from 2 to 10 years depending on the size and complexity of the trial. Successful completion of a trial involves the concerted effort of literally hundreds of scientists, clinicians, analysts, and support personnel; and the cost can reach tens of millions of dollars by the time a trial is completed and its results disseminated. Therefore, the decision to undertake a clinical trial is not made without considerable deliberation. Often, a small pilot trial is used to determine the feasibility of, and gains to be expected from, a larger trial.

Throughout the course of any clinical trial, its progress and results are monitored by a board of objective, uninvolved experts. Results of the trial, however, are not revealed until some significant result is achieved or until the trial has run its full, allotted time course.

Hypertension Detection and Follow-up Program
—Systematic care benefits even "mild" hypertensives

Published data from the Veterans Administration Cooperative Study of Hypertension demonstrated that reduction in morbidity and mortality could be attained by treating men with fixed diastolic blood pressure over 105 mm Hg. Similar trends occurred for those with fixed diastolic blood pressure between 90 mm Hg and 104 mm Hg. Results and current trends from other studies supported these findings. However, prior to completion of the Hypertension Detection and Follow-up Program, it was not known whether antihypertensive therapy was warranted for those with "mild" hypertension, and whether making use of existing medical knowledge could significantly reduce morbidity and mortality from hypertension in communities.

The primary hypotheses tested by this clinical trial were that blood pressure control in mild hypertensive patients (diastolic pressure 90 mm Hg to 104 mm Hg) is clinically justified, and that intensive blood pressure control under stepped care can significantly reduce morbidity or mortality compared to that under referred care. Stepped care is that method of treatment in HDFP clinics in which a diuretic is given initially and additional antihypertensive agents are added if necessary in a time-structured, stepwise fashion until goal blood pressure is achieved. Referred care represents referral to private physicians and other existing community sources of care. Participating in this study were 14 clinical centers, a coordinating center, EKG center, central laboratory, and monitoring laboratory.

Dramatically, HDFP showed that systematic effective management of hypertension has great potential for reducing mortality for the large numbers of people in the U.S. population with high blood pressure, including those with "mild" hypertension. Blood pressure control was consistently better for the stepped care group than for the referred care group.

Five-year mortality from all causes was 17 percent lower for the stepped care group than for the referred care group, and 20 percent lower for the stepped care subgroup with entry diastolic blood pressure of 90 mm Hg to 104 mm Hg than for the corresponding referred care subgroup. For white men, black men, and black women and for all age subgroups tested, 5-year death rates from all causes were substantially lower—by 15 to 28 percent—for the stepped care subgroup than in the referred care subgroup. These results, which show a clear advantage for systematic care, become especially significant when one considers the improved routine care of high blood pressure that has been provided in American communities in recent years.

Hypertension
—Tests of the long-term effects of captopril hypertension regulation

Captopril is an orally effective angiotensin converting enzyme which has recently been shown to be effective in the long-term control of essential high blood pressure. The addition of hydrochlorothiazide (a diuretic) produced a further lowering of blood pressure and the combined treatment produced satisfactory control in 17 hypertensive patients for an 8-month period. The hypotensive action of captopril appears to involve inhibition of the renin-angiotensin and kallikrein-kinin systems locally within the kidneys or blood vessels. The addition of captopril to diuretic therapy also appears useful in preventing the secondary hyperaldosteronism and the resultant hypokalemia that follow diuretic administration. Thus this method has the added benefit that it eliminates the need for potassium supplements, which are commonly prescribed during long-term diuretic treatment of hypertension. Captopril has another advantage in not having the toxic side effects associated with other inhibitors of the renin-angiotensin system. However, a number of troublesome side effects of captopril therapy have been reported, such as skin rash, an excess of serum proteins in the urine, loss of taste, a decrease in the number of granulocytes, and increased heart rate, the hazards of which require further assessment. Whether the hypotensive effect of captopril is due to inhibition of the renin-angiotensin system at vascular or kidney sites remains to be investigated.

Aspirin-Myocardial Infarction Study
—No benefit shown for aspirin

It has been postulated that thrombosis plays a major role in the late stages of coronary artery occlusion. Platelet aggregation is a large component in the formation of the arterial thrombi. Theoretically, an agent that prevents the aggregation of platelets would be of value for people with coronary artery disease. Aspirin, in small doses, inhibits platelet aggregation for prolonged periods of time, and therefore might be expected to prevent or retard the occlusion of coronary arteries. This would be reflected in a decrease in the incidence of myocardial infarction and a decrease in mortality due to coronary artery disease.

Several studies have given preliminary evidence that regular administration of aspirin may be of benefit to patients with known coronary artery disease. An NHLBI-sponsored study, the Coronary Drug Project, ran a pilot trial of aspirin and placebo in men with previous myocardial infarctions. Preliminary results from this trial demonstrated its promise and feasibility and led the NHLBI to sponsor a more definitive controlled study of the benefit

of aspirin in the secondary prevention of coronary heart disease.

This clinical trial, the Aspirin-Myocardial Infarction Study (AMIS), clearly indicated that the regular administration of aspirin did not reduce 3-year mortality in patients with a history of myocardial infarction. Although data indicated that aspirin perhaps is helpful in reducing the frequency of nonfatal myocardial infarction, they also showed that the drug leads to an increased incidence of side effects. On the basis of AMIS results, aspirin is not recommended for routine use in patients who have survived a heart attack.

Coronary Heart Disease
—Clinical trial evaluates effects of bypass surgery

The NHLBI Coronary Artery Surgery Study is continuing to gather and analyze data on almost 25,000 patients who have undergone coronary angiography and is comparing data on those who have and have not undergone coronary artery bypass surgery. While results are not final, several interim findings have major significance. One analysis has characterized the safety and complications of coronary angiographic diagnostic procedures and another has provided information on the limitations and incremental information to be derived from the diagnostic exercise tolerance test. It is already known that coronary bypass surgery is generally of benefit to persons who have angina pectoris that is unresponsive to intensive medical (pharmacologic) management. It has also been shown that patients with a substantial narrowing of the left main coronary artery show a statistically significant increase in life expectancy after surgery. Further evidence is required to determine whether life expectancy is improved in patients with other forms of coronary disease and whether an improvement in angina pectoris is also associated with improved life expectancy. The Coronary Artery Surgery Study will continue to explore these issues.

Chronic Obstructive Lung Disease
—Oxygen therapy: effect on mortality

A recently completed clinical study has established that 12-hour nighttime oxygen is not as beneficial as continuous oxygen therapy in extending life in patients with severe respiratory impairment, a finding that potentially could affect the approximately 500,000 Americans suffering from this condition.

In advanced chronic obstructive lung disease, a term that encompasses both emphysema and chronic bronchitis, the lung can no longer provide enough oxygen from air to meet the metabolic requirements of the body. This oxygen deficiency, which results in such complications as irritability, an increase in the number of circulating red blood cells, and elevated pressures in the pulmonary artery, can be overcome with the use of oxygen therapy.

The study, which involved six medical centers and 203 volunteer patients, was undertaken because there was some preliminary evidence indicating that administration of oxygen for 12 hours at night, when the deficiency is most severe, was as effective as continuous oxygen therapy in preventing complications. Since continuous therapy is both costly and inconvenient for ambulatory patients, 12-hour oxygen therapy appeared to be an attractive alternative. The study, which followed patients randomly assigned to either continuous or nighttime oxygen therapy for 1 to 3 years, examined not only mortality, but also many of the physiologic and neuropsychologic factors affecting the quality of a patient's life.

The results indicated that mortality was twice as great among patients in nighttime oxygen therapy as among those in continuous therapy. After the patients had received 12 months of therapy, mortality was 11.9 percent in the continuous oxygen group and 20.6 percent for those receiving nighttime therapy. For those patients followed for 2 years, mortality was 22.4 percent and 40.2 percent respectively.

Although the results obtained for the other parameters were less clear-cut and require further analysis, it appears that patients with the most severe respiratory impairment benefited most from the continuous oxygen therapy. Thus, despite 12-hour nocturnal oxygen therapy's being less costly and more convenient, the overriding consideration of mortality would make continuous oxygen therapy the therapy of choice, at least for those patients suffering very severe respiratory impairment.

Diffuse Fibrotic Lung Disease
—Use of drug adjunct in treatment

The fibrotic lung disorders represent 15 to 20 percent of the noninfectious disorders of the lung. Idiopathic pulmonary fibrosis, one of the 10 general groups of fibrotic lung disorders, is a chronic, devastating illness resulting in death in an average of 4 to 5 years from the onset of symptoms. Although 5 to 10 percent of patients respond to corticosteroids, there is no known treatment for the remainder. As part of its program of study of interstitial lung disease, the NHLBI Pulmonary Branch had conducted a trial examining the use of the drug azathioprine as an adjunct to the corticosteroid prednisone. Thirty patients were randomized to receive either prednisone alone or prednisone plus azathioprine. Although analysis is under way, early results appear to show that azathioprine is of no benefit and, because of its increased toxicity, should not be used in the treatment of idiopathic pulmonary fibrosis.

Hemophilia

—Therapy with prothrombin complex concentrates

The development of Factor VIII antibodies in a hemophiliac makes management of bleeding episodes extremely difficult. Therapeutic approaches such as steroids, exchange transfusions, bovine and porcine Factor VIII, and immunosuppressive agents generally have not been successful. Since the first reported treatment of a patient with prothrombin complex concentrates (PCC) over 10 years ago, the therapeutic efficacy of those agents has been an issue of increasing debate.

In a recent study, a group of patients with severe or moderately severe hemophilia A complicated by the presence of a well-characterized Factor VIII antibody were studied in a randomized, double-blind trial comparing two commercial PCC's and an albumin placebo. Acute hemarthrosis of the elbow, knee, or ankle was treated with a single dose of test material and assessed 6 hours later. Joint mobility improved in 34 percent of patients treated with PCC, compared to 18 percent of those given the placebo. Also, joint pain had decreased in 49 percent of patients treated with PCC, compared to 25 percent of those receiving placebo. These data indicate that PCC, when used in a single dose, is partially effective in the treatment of hemarthrosis in hemophiliacs with Factor VIII inhibitors. In the absence of other effective and readily available forms of therapy, PCC use in these patients will be continued.

Granulocyte Transfusion Study

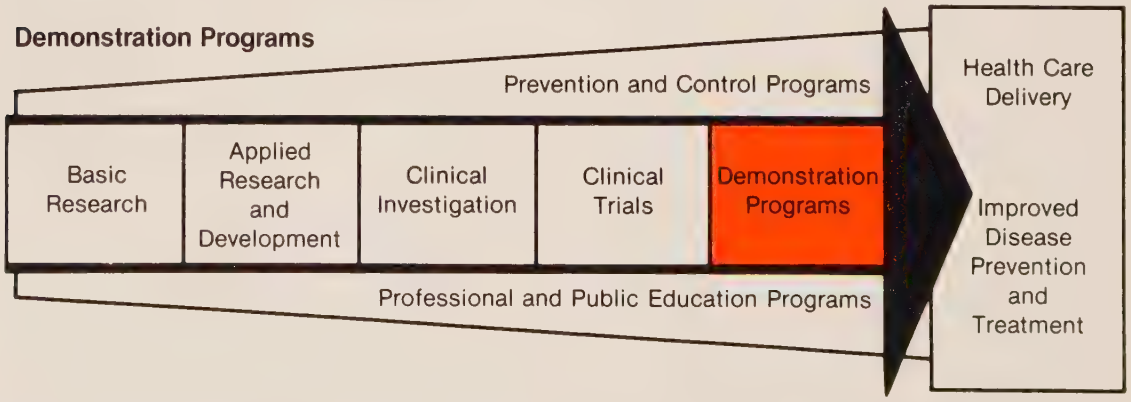
—Use of granulocytes for prevention and treatment of infection

Infection due to suppression of the body's natural defense mechanisms remains a major cause of death in patients receiving chemotherapy for malignant diseases. One approach to the problem of septicemia and high mortality in these patients is the therapeutic use of granulocyte transfusions. Recent improvements in collection techniques, employing continuous flow centrifugation, now permit the collection of granulocytes from a single, normal donor in sufficient numbers to study their application in the treatment of infections in granulocytopenic patients. Recent studies have demonstrated the efficacy of granulocyte transfusions as an adjunct in the therapy of septicemia due to gram negative microorganisms associated with granulocytopenia.

The aims of the recently completed Granulocyte Transfusion Study were to determine (1) whether infections can be prevented in patients who receive granulocytes prophylactically and (2) whether recovery from infection is aided in patients who receive granulocytes therapeutically.

The prophylactic trial was performed to evaluate the role of granulocyte transfusions during first remission induction chemotherapy for acute nonlymphoblastic leukemia. More than 100 uninfected patients were randomized to receive or not receive daily transfusions for up to 28 days when blood granulocytes fell below a prescribed level (500 per microliter). Prophylactic granulocyte transfusions decreased the incidence of bacterial septicemia, but they failed to affect the overall incidence of infections, rate of marrow recovery, success in achieving complete remission, or mortality. Most patients experienced transfusion reactions, and the incidence of pulmonary infiltrates was increased in transfused patients. The study concluded that prophylactic granulocyte transfusions as currently given cannot be recommended as standard therapy during remission induction for this type of leukemia. This finding is of considerable importance because it permits substantial saving in cost, effort, and scarce resources without compromising patient care.

Data from the therapeutic trial, involving the randomization of approximately 50 patients into treatment and control groups, are undergoing statistical analysis, and results soon will be available.



Demonstration programs test methods to introduce or facilitate delivering health care advances to the public. Demonstration activities, which are a recent addition to the Institute's programs, have been implemented to effectively translate research findings into health practices. Such programs will be of even greater importance as more clinically applicable information becomes available for dissemination from ongoing clinical trials.

Hypertension
—Recommendations of Black Health Providers Task Force being implemented

NHLBI, in concert with the Health Services Administration, is supporting a five-site demonstration program to develop model systems of high blood pressure control in black and Hispanic communities. The lessons learned in the Hypertension Detection and Follow-up Program will be incorporated into the demonstration program.

The program, announced by the Secretary of Health and Human Services in August 1980, will be located in four predominantly black communities (two urban and two rural) and one predominantly Hispanic community. Such a demonstration program was one of the key recommendations of the Black Health Providers Task Force on High Blood Pressure Education and Control, which was commissioned by NHLBI in October 1977 and submitted its report to NHLBI in July 1980. The Institute, working with the provider groups represented on the task force, is giving widespread circulation to the report and its more than 80 recommendations. A number of the recommendations will be addressed by NHLBI, whereas others are being brought to the attention of appropriate agencies or organizations according to their respective mandates and responsibilities.

Hypertension
—Gains in high blood pressure education and control

The National High Blood Pressure Education Program (NHBPEP) is a national cooperative effort to reduce death and illness by educating professionals, patients, and the public about high blood pressure. It is coordinated and staffed by the NHLBI and involves numerous Federal agencies, state health departments, and more than 150 private-sector organizations. The current initiatives of the program are revision of treatment recommendations for physicians, overcoming barriers to cooperation among health professionals, improving dietary management of high blood pressure, improving interaction between patients and health professionals, and assisting in developing better high blood pressure control in rural communities and in work settings. In addition, the program maintains a core of activities including an information center, technical assistance at the state and local levels, and materials development.

A survey performed in 1973 to assess public knowledge about high blood pressure and help plan educational activities for the NHBPEP was repeated in 1979. The findings show clear and striking changes in the public's understanding of hypertension. In 1979, 73 percent of the public, compared with 63 percent in 1973, believe hypertension is a serious condition. Between 1973 and 1979, the segment of the public having their blood pressure measured within the prior year increased from 73 to 83 percent. Other results indicate that nearly twice as many people now know what a normal blood pressure is, and 40 percent more people now understand that hypertension does not have reliable symptoms. In addition, more people believe effective treatment is available for hypertension; likewise, greater numbers of patients are following their prescribed therapy. Preliminary data analysis also indicates that stroke death rates, which have declined precipitously in the United States since the NHBPEP began are measurably lower over time in communities that have active education programs than in those that do not.

Recent NHBPEP activities have been directed toward communicating to the health care community lessons learned from the Hypertension Detection and Follow-up Program. The *Report of the Joint National Committee on Detection, Evaluation, and Treatment of Hypertension* provides general guidelines for the physician that, for the first time, address drug and dietary treatment of so-called mild hypertension. Similarly, an NHBPEP working group is identifying critical patient behaviors and how they relate to the education of people about dietary control of high blood pressure. Because the HDFP showed dramatically that even patients with borderline hypertension benefited from antihypertensive therapy, "mild" would appear to be a misleading label for this range of high blood pressure. Thus, the NHBPEP is bringing together another working group to consider a redefinition of hypertension (traditionally specified, and recognized by the World Health Organization, as 160/95 mm Hg), particularly to assign different names to categories of hypertension.

Hypertension
—Local television productions

The Institute has completed production of a pilot series of television announcements on hypertension. These programs have been designed to be inexpensively adapted and produced by local television stations for use in existing broadcast shows dealing with health topics. The pilot programs, consisting of videotapes, scripts, and questions and answers, have received enthusiastic response by stations in five test cities: Petersburg and Fredericksburg, Virginia; Charlotte, North Carolina; Baltimore; and Pittsburgh. Following a meeting with station representatives in these cities, the programs are undergoing final revisions and soon will be available for marketing nationwide through the national and local high blood pressure programs.

Nutrition
—Cooperation with the American Heart Association

In collaboration with the American Heart Association (AHA) and other groups, NHLBI is sponsoring projects to transfer state-of-the-art knowledge about nutrition to health professionals and members of the lay public. The Institute has completed a year-long education project in cooperation with a

major supermarket chain in the Washington, D.C., area and is working with the AHA to adapt the program and make it available to the Association's chapters across the country. The "Foods for Health" program attempted to demonstrate the usefulness of placing helpful nutrition-related information at the point of purchase—the grocery store—where consumers make the decisions that affect their diet. The program featured a series of biweekly "Eaters' Almanacs," which provided basic dietary advice, suggested recipes, and other information related to heart disease. Data from the program are being analyzed to evaluate the feasibility and impact of communicating point-of-purchase health information, and several other grocery chains, businesses, and health- or nutrition-oriented organizations are in the process of developing and implementing the program in their service areas. The AHA has already distributed another pilot project of NHLBI—"Food for Thought"—a game designed to be played in the cafeteria setting for the same purpose, to influence decisions at the point of purchase.

Also with the AHA, the Institute is sponsoring workshops on nutrition counseling for health professionals. The objective of these workshops is to disseminate up-to-date information on effective nutrition counseling skills to practitioners at the local level in the most cost-effective manner possible. At the conclusion of the workshops, a model "package" containing guidelines, materials, and videotapes will be assembled to allow similar workshops to be conducted by AHA chapters nationwide.

Health Education

—Pretesting TV/radio messages

Pretesting is widely used by commercial marketers to evaluate advertisements for products and services before commitments are made for final production. Recognizing the value of pretesting radio and television health messages in the early stages of development, the NHLBI is collaborating with the National Cancer Institute to administer the Health Message Testing Service. This standardized, cost-effective, and reliable testing technique can help message producers assess the ability of a message to attract attention; recall of important ideas; whether a message is considered personally relevant, believable, interesting, and informative by the target audience; and diagnostic indications of message strengths and weaknesses.

To utilize the testing service, health message producers submit a prefinished TV or radio spot or printed document to NIH message testing staff who review it and schedule a test date. Testing is conducted with 300 respondents in three geographically diverse cities. These respondents, representatives of the target audience for whom the final message is intended, are recruited by randomized mailings inviting them to preview and evaluate new television or radio programs or educational publications. All questions administered by message testing staff during the preview session are developed in consultation with the health message producer and, in a departure from commercial testing, respondent self-perceptions about health are used as variables in analyzing responses to health messages. Results of this audience evaluation will either assure the producer that the message is being perceived as intended or that the spot or publication requires modification while there is still time to do it inexpensively. NHLBI, for example, has used the testing service in development of public service announcements for the National High Blood Pressure Education Program. An Institute booklet on exercise and health was the first printed document to undergo testing.

The Office of the Assistant Secretary for Public Affairs has recognized the Health Message Testing Service as a valuable service and intends to expand it to provide the same cost-effective function to other programs of DHHS.

Asthma

—Improved self-management of asthma in children

As a result of recent developmental research in asthma self-management, satellite communications have been extended to the area of patient education. Researchers at the National Asthma Center in Denver have completed a pilot project which uses a two-way satellite-mediated system to help an asthma self-management program at the National Asthma Center. In the pilot project, a group of parents of asthmatic children gathered for three evenings in a rural health clinic in Trinidad, Colorado, 250 miles south of Denver. They were led in a group discussion of their common problems related to asthma by a psychologist located in Denver. The psychologist and the parents could see and hear each other through a television screen. The educational program focused on teaching the parents skills in managing their children's asthma and using the experience of other parents to learn ways of coping with this health problem. In a separate room, a health educator worked directly with the children to teach them ways of coping with their asthma. The educational program has been enthusiastically received by both parents and children. Evaluation of the program will include the examination of its effects on the number and severity of asthma attacks, rate of hospitalization for asthma, days of school missed, and cost of medical care.

Although satellite-mediated systems have been used for several years in the education of health professionals, the current program is one of the first to use the system for *patient* education. Since there are public service satellite systems already in operation with programs that may be received by hospitals and private homes, the potential for reaching thousands of asthmatic children and their parents with education on asthma self-management has been greatly expanded. The development and use of effective educational programs through these

systems offers the possibility of reducing health care costs as well as alleviating the suffering of asthmatic children.

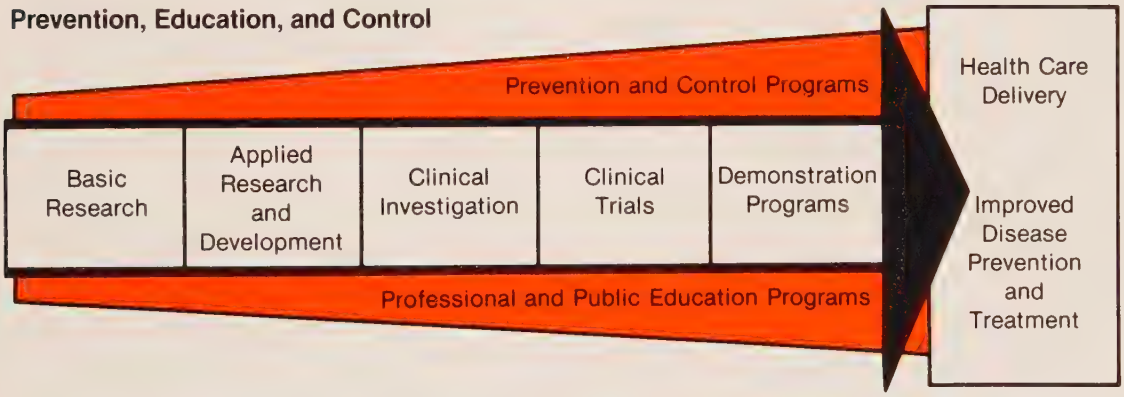
Sickle Cell Disease
—Assisting teachers in classroom education

Now in its second year, the Health/Science Teacher Training Seminar program is designed to introduce concepts about sickle cell disease at the high school level and encourage regional, state, and local organizations to promote educational programs. The program utilizes the professional expertise of faculty members selected from conveniently located colleges, universities, and medical schools to conduct training sessions in physiology, biochemistry, genetics, and medical manifestations of sickle cell disease. A special section of each seminar is devoted to teaching methods and materials to help trainees incorporate the concepts learned and the teaching aids provided into their own teaching curricula. Tests administered to attendees before and after seminars indicate a dramatic increase in understanding of concepts and total knowledge gained regardless of the teaching level, specialty, or background of the participants. Sixteen seminars attended by more than 400 teachers were conducted throughout the country during the past year. It is estimated that through the multiplier effect of teacher training, some 60,000 students will benefit directly from the factually accurate content of these seminars. About 25 additional seminars are planned for the current year.

Clinical Trials
—Varied techniques used to disseminate latest clinical information

NHLBI uses a wide variety of communication techniques to convey the most recent information concerning improved methods of clinical care. The Institute produces publications for both lay and professional audiences and develops films, exhibits, public service television and radio spots, transit posters for airports and buses, press conferences, and presentations for television "talk" shows. The varied approaches recently used for communicating findings of the Hypertension Detection and Follow-up Program are excellent examples. In releasing these findings, the Institute held press conferences, initiated contact with magazine and newspaper columnists, briefed feature writers for lay magazines and Sunday supplements, and promoted the program to producers of television "talk" shows. This variety of approaches has allowed the Institute to reach a much larger audience and to communicate the implications of a major clinical trial to millions of citizens.

Prevention, Education, and Control



Clearly, the ultimate focus of the biomedical research spectrum—shown by the direction of the arrow in the diagram above—is improved prevention, education, and treatment of the cardiovascular, pulmonary, and blood diseases for which the Institute has responsibility.

Through the efforts of investigators at all levels of the research spectrum, several advances have emerged which offer great potential for the treatment and prevention of disease.

Atherosclerosis
—Analysis of nutrient content of common American foods

Diet is considered a significant factor in the development of atherosclerosis and subsequent coronary heart disease. However, studies of nutritional factors must depend on data on the nutrient composition of common foods in the American diet.

Through a recent interagency agreement with the Department of Agriculture, NHLBI is developing and making available such data. The objective is to provide accurate, up-to-date comprehensive information in a useful form on the composition of food with essential nutrients. Analyses are determining such things as the fiber content of ready-to-eat breakfast foods, the content of fatty acids

tocopherol and sterol, the lipid composition of beef and pork, the nutritional role of organic forms of chromium, sugar and carbohydrate content of breakfast cereals and soft drinks, and numerous others.

Hypertension
—Symposium addresses high blood pressure in the young

Identifying and modifying risk factors at early ages are important aspects of cardiovascular disease prevention. During the past 3 years, NHLBI has supported research concerning the identification of precursors and associated correlates of hypertension in the young.

Investigators recently held a symposium to discuss the difficulty of defining blood pressure norms in children, methods to evaluate genetic and environmental influences, blood pressure "tracking," and correlates of blood pressure. Although the clinical implications of blood pressures in the upper percentiles in the young must be interpreted with caution, the symposium found that recognizing blood pressure correlates such as body size suggests therapeutic options that may be introduced at an early age.

Hypertension
—Public school programs stress health education

Annually, the Federal Government provides millions of dollars for projects to communicate health messages, yet few models for health education programs in the public schools have been developed. A new NHLBI effort is stressing cooperation with the Department of Education and the Center for Disease Control to develop school health programs aimed at hypertension control.

Within NHLBI a full-time position has been created to develop educational programs and to serve as liaison with the Department of Education and the Center for Disease Control. The goal is to develop an effective public school curriculum that will present up-to-date knowledge in the area of heart, lung, and blood diseases. In addition, both NHLBI and the National Cancer Institute are supporting development of a school program titled "Know Your Body." The project is testing the effectiveness of interviewing when school children are at increased risk because of nutritional, blood pressure, smoking, or obesity problems.

Hypertension
—Information to increase public awareness of high blood pressure

In the area of heart disease, the NIH "Medicine for the Layman" series has recently published information concerning awareness and control of high blood pressure. Like the other publications in this series, the hypertension materials are worded for the general public without complex medical terminology. They are attractively illustrated and address topics of special concern to disease prevention. The hypertension materials explain how blood pressure is measured, what pressures are considered normal, and how high blood pressure decreases life expectancy. The importance of elevated blood pressure as a risk factor for stroke, kidney problems, and heart disease is given special emphasis, and therapy to control blood pressure is carefully explained.

A question and answer section treats issues of common interest such as the importance of diet and exercise, the effects of coffee and alcohol, the importance of smoking, how hormones are related to blood pressure, and many other topics.

Hyperlipoproteinemia
—Handbook for dietary management

To assist doctors, nutritionists, and others dealing with patients with high blood levels of lipoproteins, the Institute has developed a publication package on dietary management of hyperlipoproteinemia. The package uses a combination of approaches including a handbook for the practitioner and five different pamphlets for patients with particular blood-lipid disorders. In 1979 alone, almost 430,000 copies were distributed by means of a selective targeted approach. Copies have been provided to health professionals who have a distinct need for them. These professionals, in turn, distribute materials to those patients who need information to guide their diet program. The General Accounting Office recently cited this project as an example of efficient health education communications.

Nutrition
—Diet and health education

Relationships between dietary habits and prevention of cardiovascular diseases is less well-established than the relationship between blood pressure control and the prevention of its complications. For example, sodium, fat, and excessive body weight in most individuals exert a demonstrable adverse effect on blood pressure, blood lipid levels, and glucose tolerance. It has not yet been conclusively shown, however, that lowering the amount of sodium, dietary fat, and calories in the population at large can help prevent the disease for which these are implicated as risk factors. Thus, the NHLBI is supporting research to provide more precise causal links between specific dietary factors, such as saturated fats and sodium, and major cardiovascular diseases, such as atherosclerosis and hypertension.

While these validation studies continue, the Institute is committed to act on available knowledge to promote healthful nutritional practices among Americans. This goal is being pursued through an ongoing Institute activity to develop public information and education methods relating to nutrition

and heart disease. Actively collaborating with NHLBI in this effort are influential organizations such as the food industry, the mass media, education systems, and voluntary health groups, as well as other branches of the Federal Government.

Heart Attack
—Information for the layman

Throughout contemporary medicine, there is an emerging consensus that the decisions of individual persons play an enormous role in maintaining good health. Recognizing the importance of providing information to encourage intelligent decision-making, NIH has created a lecture series featuring distinguished physician-scientists. The series of lectures and their publications are designed to help people learn more about their bodies and what one can do to maintain or improve one's health.

One recent publication, based on the "Medicine for the Layman" series, is directed at primary and secondary prevention of heart attacks. The publication presents basic physiologic and clinical information in an interesting and attractive format that gives readers an overview of how the heart functions and how it becomes subject to heart attacks. The publication describes pathophysiology, symptoms, what to do, and where to go for help. In addition, the publication describes major therapies currently in use, how these therapies improve heart function, and what their limitations are. In a special prevention section, the publication discusses such risk factors as smoking, high blood pressure, cholesterol, diabetes, sedentary lifestyles, and obesity. All of these are factors that can be controlled by personal decisions, and the publication stresses practical means of lessening exposure to risk factors. A question and answer section addresses commonly held conceptions about therapy and prevention, and points out validated and unvalidated approaches to maintain cardiovascular health.

Occupational Health
—Epidemiology seminar for occupational physicians

NHLBI, in cooperation with the American Occupational Medical Association (AOMA) cosponsored a pilot seminar in epidemiology for occupational health physicians in February 1980. The impetus for this seminar was the realization that the work setting offers a number of advantages for successful health promotion and cardiovascular disease risk reduction.

Although there are advantages in having health promotion and disease intervention programs in the work setting, problems exist in planning the most appropriate programs for this population. One problem stands out above the others: medical data collection and analysis. Therefore, NHLBI and AOMA joined together to cosponsor seminars in epidemiology for occupational health physicians.

NHLBI provided the faculty and staff to develop the curriculum and evaluation component and teach the seminar, with a faculty of six biostatisticians and epidemiologists experienced in the health problems of workers. AOMA will continue to manage the seminars, the second one to be held in February 1981.

The Lung
—Booklet aimed at disease prevention

Another of the recent publications based on the "Medicine for the Layman" series is aimed at prevention of pulmonary diseases. Similar to the series publication on heart attack, this approach uses a readable and attractively illustrated format to give basic information on how the lungs work, what disorders they are susceptible to, and how lung disease can be treated or prevented. Current methods of diagnosis are explained and risk factors are discussed in light of what one can do to prevent lung disorders and to recognize the early symptoms of pulmonary disease. A question and answer section addresses common public interests such as: Is it safe to have chest X-rays more than once a year? Can hair sprays damage the lungs? What kinds of heating systems are least harmful to the lungs? and many others.

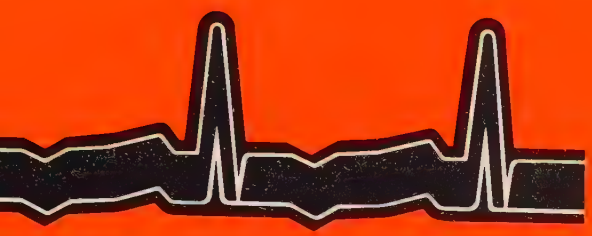
Chronic Obstructive Lung Disease
—New program to improve physicians' and consumers' abilities in assessment

NHLBI has recently undertaken the design of a program to enable practicing physicians to make better quantitative assessment of an individual's risk of chronic obstructive lung disease. This program involves development of an assessment index to enable the physician to recommend appropriate intervention and to encourage patient compliance. The planned index takes into account such variables as age, sex, socioeconomic status, smoking and drinking habits, exposure to airborne pollutants, and hereditary and family factors. The index will be made available as a part of continuing education programs for physicians and allied health personnel. A similar educational effort will be made with patients. For the patient, an index will be provided to allow assessment of personal risk of developing chronic obstructive lung disease. It is hoped that the patient assessment index will provide improved motivation to eliminate risk factors such as smoking.

Cooley's Anemia
—New booklet available to public

Cooley's anemia is a severe inherited blood disorder that occurs primarily in persons of Greek, Italian, and Oriental ancestry. Recognizing the need for public education concerning this serious but little-known disease, the NHLBI has prepared a new information booklet, *Cooley's Anemia: Prevention Through Understanding*, for distribution to physicians and the interested lay public. Produced in

cooperation with the Cooley's Anemia Foundation, Incorporated, the booklet discusses the various forms of thalassemia, of which Cooley's anemia is one; the cause and inheritance patterns of the disease; the symptoms and effect on victims of Cooley's anemia; treatment and its side effects; prevention, including identification of carriers, prenatal testing, and genetic counseling; and current research activities and needs. A glossary of terms is also included for additional explanation and quick reference. Physicians interested in the current status of research and treatment relating to Cooley's anemia are advised to request a copy of the NHLBI publication, *Assessment of Cooley's Anemia Research and Treatment,* which discusses these topics in greater depth.



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Special Emphasis Areas for 1980

Special Study Groups: Attacking Problems in Arteriosclerosis, Hypertension, and Black Health Care

To assess the health needs of the Nation and formulate programs that permit optimal use of its resources, NHLBI regularly seeks information and advice from scientists and other experts in the community at large. Whereas the Institute's Advisory Council and specific advisory committees provide recommendations on a regular basis, special study groups are established when appropriate to analyze particular problems with a view to achieving specified objectives. The Working Group on Arteriosclerosis and the Hypertension Task Force are examples of such groups, which during the past year contributed significantly to our understanding of two widespread and challenging diseases. A third group, the National Black Health Providers Task Force on High Blood Pressure Education and Control, considered a wide range of issues related specifically to the reduction of high blood pressure among black Americans.

Working Group on Arteriosclerosis

During the past decade, NHLBI has initiated major activities to assess the state of knowledge and opportunities for research in arteriosclerosis, beginning with the 1970-1971 Task Force on Arteriosclerosis. In 1977, the first Working Group on Arteriosclerosis was charged with determining the extent to which the 1971 task force report had been and was being put into effect. The working group recognized that much scientific progress and advice had been successfully translated by Congress into mechanisms for coping with this major disease of mankind. However, in the course of fulfilling its assignment, the working group repeatedly encountered topics in research in atherosclerosis that merited detailed consideration but were beyond its charge. Therefore, it concluded unanimously that the time was ripe for a second task force that would help to redefine goals and priorities for research into the causes, prevention, and treatment of atherosclerosis.

In response to this recommendation for a second task force, the currently active Working Group on Arteriosclerosis was appointed in the fall of 1978. Among its topics for consideration were a number of questions that arose but could not be settled by the 1977 working group within the confines of its charge and alloted time:

- Are the new directions in research receiving a share of national support proportional to their potential impact on current understanding of atherosclerosis and the magnitude of the problem?
- Are activities that began years ago living up to current expectations?
- Are new opportunities being recognized and actively explored?
- Is research involving problems in U.S. subpopulations (e.g., the unique problems of cardiovascular disease in the black population) receiving appropriate attention?
- Should current priorities be the same as those of 1971?
- Are there new fruits of research that are ready for clinical validation or practical application?
- Should NHLBI play a larger role in public education and in dissemination of information concerning risk factors?
- How does the national commitment of resources for atherosclerosis relate to commitments for other health problems?
- Does public policy concerning atherosclerosis reflect the present understanding of prevention, early detection, and management of the disease?

As indicated, research relating to arteriosclerosis and its complications encompasses a variety of disciplines and opportunities—basic and clinical and community-oriented—aiming to prevent disease or seek improved treatment. During the past year, the new working group solicited information from a spectrum of expert witnesses. In meetings with members of the working group and other consultants, these experts discussed current knowledge and opinion and documented their findings in summaries written for the working group. Specific recommendations for research in arteriosclerosis are being drafted and discussed by members of the various subgroups for publication in the final report of the full working group.

Hypertension Task Force

The objectives of the Hypertension Task Force, charged in September 1975 with assessing the current state of hypertension research, were to:

- Summarize current knowledge about the mechanisms of hypertension;
- Identify promising areas of research now receiving little attention; and
- Assess future research needs, pinpointing problems that require greater emphasis.

The task force consisted of 20 members, most of whom served as chairpersons of 12 subgroups. Each subgroup, which included 4 to 10 participants, assessed a particular aspect of hypertension research related to etiology and pathogenesis, specifically:

- Local hemodynamics
- Neural control of the circulation
- Vascular smooth muscle: nerve terminals
- Hypertensive vascular disease
- Vascular smooth muscle: contractile apparatus
- Pediatrics
- Genetics
- Prostaglandins
- Kallikrein-kinin
- Renin-angiotensin-aldosterone
- Salt and water.

The task force also heard reports from specialists on topics pertaining to hypertension that had not been assigned to a subgroup. Such topics included the relation between high blood pressure and obesity, hypertension and pregnancy, and the role of the Food and Drug Administration in antihypertensive drug therapy. The 150 scientists who served on the task force and subgroups and the special consultants were all recognized as experts on particular hypertension-related research topics.

The work of each subgroup consisted of preparing a report that fulfilled the objectives of the task force. The final reports set forth the recommendations of a specialized group as modified and refined in the light of insights provided by an interdisciplinary approach. Each report was then reviewed by a specialist in the pertinent field of study who was not a member of the subgroup.

The general recommendations of the task force were discussed in five categories: research, manpower, animal models, resources and technology, and Federal support for research.

In view of the multifactorial nature of hypertension, members of the task force identified seven areas of research that merit particular emphasis:

- The role of sodium in the activity of vascular smooth muscle and in the regulation of fluid volumes, hormonal systems, nervous system function, and blood pressure. [Until more facts become available, the task force recommended that restraint be exercised in sodium consumption, specifically: (1) avoidance of overly salted prepared foods, (2) cooking with only small amounts of salt, (3) not using the salt shaker at the table, and (4) reducing the amount of sodium added to baby foods.]
- The function of the nervous system, especially the central nervous system, in the regulation of normal arterial pressure and pathogenesis and treatment of hypertension.
- The influence of local modulators of resistance (e.g., the renin-angiotensin system, the kallikrein-kinin system, and the prostaglandins) on blood pressure.
- The role of the microcirculation and veins in the development and maintenance of hypertension.
- The study of blood pressure regulation, hypertension, and antihypertensive therapy during growth and development of the child.
- Genetic mechanisms of hypertension.
- The mechanisms responsible for the changes in small arteries and arterioles that cause the increase in total peripheral resistance of chronic hypertension. Whether the increase is due primarily to a change in active contraction of vascular smooth muscle or to a structural increase in vessel wall thickness is a major question.

Citing the pivotal role of research in the future prevention and/or control of hypertension, the task force recommended that a steady supply of scientists from a variety of disciplines be encouraged to contribute to hypertension research. Stable programs of support for training must also be a high priority, the group concluded.

Concerning animal models, the task force recommended further development of a genetically hypertensive nonhuman primate model and use of nonhuman primates in specific research areas such as the effects of salt intake on blood pressure.

The group also pointed to the need for animal models to study the relationship between obesity and hypertension, hypertension in pregnancy and the effect of hypertension on fetal and neonatal development, and factors associated with high blood pressure in children.

In the area of resources and technology, the task force reported that all areas of hypertension research would be facilitated if important resources were made available to investigators. The resources required include unique equipment, central pools of chemical and pharmacological tools, and standard reagents. Provision of such resources would enable more individuals to carry out studies at a reduced cost and enhance comparison of data between laboratories. Implementation of the research recommendations made by the task force will also require development of new methods and improvement of existing ones.

The task force did not attempt to determine the level of increased Federal support that will be required to implement the recommendations in its report. Clearly, additional resources will be needed so that the NHLBI and other components of the NIH will be able to support all of the high-quality research relevant to the group's recommendations. The task force also stressed that additional resources should enable the support primarily of individual research project grants.

Members of the task force expressed hope that their report will stimulate hypertension research in new subject areas as well as in areas of current investigation that require reemphasis, and that their effort will focus attention on clinical opportunities that stem from full application of currently available knowledge.

Black Health Providers Task Force

Commissioned by NHLBI in October 1977, the National Black Health Providers Task Force on High Blood Pressure Education and Control conducted a 30-month analysis of issues related to the improvement of blood pressure control among black Americans. The task force presented its 88 recommendations for discussion at a White House/NHLBI-sponsored symposium in the summer of 1979. The final report was submitted to the Institute in July 1980.

In August 1980, the Secretary of Health and Human Services commended the work of the task force and announced a 5-year demonstration project to implement certain task force recommendations in four predominantly black communities (two urban and two rural) and in one predominantly Hispanic community.

The task force recommendations are based on a systems approach which defined 20-year goals for blood pressure control among blacks. The major goal was stated as follows: "Among blacks with diastolic blood pressures of 105 mm Hg and above, attain effective control (diastolic less than 90 mm Hg) among a net of 50 percent or more within the 5-year period 1981-85. Within each subsequent 5-year period (1986-90, 1991-95, 1996-2000), bring under control a net of at least 50 percent of remaining hypertensive (diastolic 105 mm Hg and above) blacks. For persons in the 90-104 mm Hg diastolic range, attain better levels of control and awareness by reducing the percentage of blacks in each of the following categories: 1) undetected hypertensives, 2) detected hypertensives, not in treatment, and 3) detected hypertensives, in treatment, not under control (control defined as less than 90 mm Hg diastolic). The rate of this reduction should result in percentages of awareness and control among blacks at the end of each 5 years equal to the percentages in the general population. The clear need for many areas of the country would be for extraordinary activity during the next 5 years (1981-85) to achieve black parity in awareness and control."

The task force urged Federal agencies to develop data acquisition processes to monitor the Nation's progress in meeting these goals. The task force recognized that the realization of its stated goals will require the active cooperation of Federal, state, and local governments; the health care provider community; and business, labor, volunteer, and civic organizations.

Recommendations were presented for the consideration of the Institute, other Federal agencies, and elements in the public, private, and voluntary sectors. These recommendations relate to the following issues:

- Provider roles
- High blood pressure education and control systems
- Community education and coordination
- Biomedical and epidemiological research
- Delivery systems—research and policy
- Nutrition
- Health education
- Behavioral studies related to hypertension
- Manpower
- Pediatric high blood pressure
- Financial barriers
- Physician assistants and nurse practitioners.

The Institute is addressing many of the task force concerns regarding professional and consumer education through the National High Blood Pressure Education Program. A number of the organizations represented on the task force have

been invited to apply for membership to the coordinating committee of the NHBPEP. Research and study recommendations have been referred to the Division of Heart and Vascular Diseases for appropriate action. Recommendations within the purview of other Federal agencies and non-Federal organizations have been forwarded to them for their consideration.

Pursuant to a request from the House Appropriations Committee, the Secretary of HHS will present a Department-wide initiative in January 1981 for responding to the recommendations of the task force. NHLBI is participating in the preparation of that initiative.

Technology Transfer: Sharing Science With Society

While the NHLBI has demonstrated remarkable achievements in research related to the Nation's most pressing health problems, it recognizes that its legislative mandate is not fully met unless research results are communicated to the health care community and adopted for the benefit of society as a whole. As knowledge is multiplied through research on disease processes and effective methods of prevention, diagnosis, and treatment, the need for transferring validated technologies to the community at large likewise grows. Throughout its history, the Institute has given careful attention to the evaluation of technology transfer processes, the development of effective means of transfer, and the implementation of its plans in conferences, workshops, publications, and other information exchange media.

The technology transfer process, viewed from the NHLBI perspective shown in figure 9, consists of six interrelated stages:

Knowledge development includes all biomedical, behavioral, and educational research directly related to the Institute's mission. This stage includes basic research, applied research and development, clinical investigations, and clinical trials, as well as the behavioral, motivational, and education research component of prevention, education, and control programs.

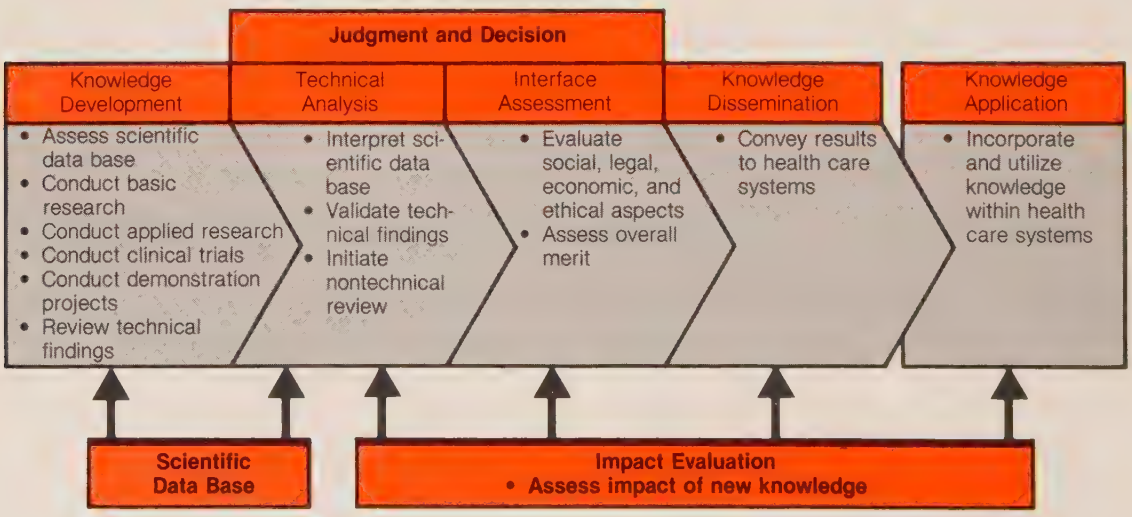
Technical analysis is a process whereby agreement is reached by most of those concerned about the soundness and feasibility of a technology. A technical analysis exercise is intended to assure that the technology or knowledge is ready for general application; that it has been validated for safety and efficacy; and, if not so validated, that the gaps in the knowledge base have been delineated. Points of disagreement as well as agreement must be recognized.

Interface assessment embodies a full consideration of the nonscientific factors involved in moving a new technology into the health care delivery system. These factors can include economic, ethical, legal, regulatory, social, and other issues, as considered by specialists from these fields and the biomedical professions.

Knowledge dissemination is the diffusion of the results of knowledge development, technical analysis, and interface assessment to the health delivery community and to the public, as appropriate, and uses both traditional and newer channels of scientific communication.

Knowledge application is the acceptance, adoption, and appropriate use of validated technologies by the health care community and by the public.

Figure 9.
Technology Transfer Process


Judgment and Decision
Knowledge Development
Technical Analysis
Interface Assessment
Knowledge Dissemination
Knowledge Application
• Assess scientific data base
• Conduct basic research
• Conduct applied research
• Conduct clinical trials
• Conduct demonstration projects
• Review technical findings
• Interpret scientific data base
• Validate technical findings
• Initiate nontechnical review
• Evaluate social, legal, economic, and ethical aspects
• Assess overall merit
• Convey results to health care systems
• Incorporate and utilize knowledge within health care systems
Scientific Data Base
Impact Evaluation
• Assess impact of new knowledge

In *impact evaluation,* the progress of an individual medical technology's movement into the health care system is monitored and evaluated, with attention given to the extent and impact of its application. The results of this evaluation are fed back to earlier stages to ensure periodic reassessment and revision of the technology as necessary.

The NHLBI is certainly not alone in its concern for promoting effective dissemination of knowledge and the timely application of research results in the health care community. The Federal Government has aided in progress toward technology transfer goals through legislation such as the 1978 Act authorizing the National Center for Health Care Technology and the NIH's 1977 initiation of a consensus development program under the Office for Medical Applications of Research (OMAR). The cornerstone of OMAR's program is consensus development, a process that brings together knowledgeable researchers, practitioners, consumers, and others as appropriate, for the purpose of achieving agreement on whether a given technology is ready for general application. The subject technology may be a drug, device, or procedure.

The consensus development program is not intended to replace the standard means of publishing research results, nor does it duplicate the intent of state-of-the-art scientific meetings. Rather, the consensus development meeting complements those activities by providing a public forum to ensure that all viewpoints are considered.

In seeking technical consensus on the soundness and feasibility of new technologies, conference panels and participants are constrained to clarify the state of the art, identify and address key issues, and enumerate points of disagreement as well as agreement. Recommendations and conclusions are published in conference summaries to provide guidance for physicians and the public; however, given the continuous, rapid changes in technology, consensus statements should be viewed simply as reflections of the best *current* thinking of the people with the best knowledge of the technology in question.

Not surprisingly, members of the research community have recognized a need to utilize the consensus development program in examining the process that spawned it: Technology transfer is an infant science with concepts, terminology, objectives, and methods that are continually growing and evolving. Even though established mechanisms of communication are available through a number of Federal programs, there is a need to refine existing knowledge of the technology transfer process and to develop new avenues for future use.

To help in achieving a clear understanding of the many complex processes of communication, NHLBI cosponsored (with OMAR) a conference entitled "Development and Dissemination of Biomedical Innovations: Foundations for Program Development." The conference, held in March 1980, brought together participants from academia, government, industry, and the health practice community to examine the major processes required for translation of biomedical advances. Drawing on their collective expertise in medicine, management, and health policy development, the 64 participants examined current knowledge and developed recommendations in the areas of:

- **Generation of ideas**—including the innovation process and its diverse contributory elements.
- **Dissemination**—with particular attention to communications patterns among basic and clinical researchers.
- **Adoption**—focusing on identifying necessary resources and incentives for biomedical development.

At the conclusion of conference sessions in each topic area, small working groups were convened to develop recommendations to address both application of current knowledge and key areas for further study.

With the knowledge gained from this conference and similar meetings to be held in the future, the Institute staff can augment the methods that have proven successful in the past. Other NHLBI-sponsored consensus development conferences of the past year are described in the following paragraphs.

Transfusion Therapy in Pregnant Sickle Cell Disease Patients

Studies to date have developed but not satisfactorily proven the value of prophylactic use of transfusion therapy for sickle cell disease patients in pregnancy, according to the recently published consensus statement from this 1979 conference. Participants were organized into four work groups to address related subject areas:

- The need for further research;
- Clinical research approaches;
- Perinatal considerations; and
- Sociomedical issues.

Work group I addressed the nature and extent of previous research on this transfusion technology and concluded that positive effects of the therapy had not been satisfactorily proven. It was the group's recommendation that further research be conducted to determine conclusively whether the treatment is effective. The second work group concluded that prospective and randomized research

is needed to define the relationship between outcome and transfusion therapy during pregnancy. A national cooperative multicenter study, which should be integrated with the 5-year natural history study, was recommended as an approach. Work group III recommended that a detailed series of clinical and laboratory procedures be used to follow sickle cell patients through the ante-, intra-, and postpartum periods and to establish a data base. The fourth work group held that unresolved ethical questions and insufficient data preclude a nationwide policy of transfusion therapy, and it recommended a limited-size study to compare the value of therapeutic transfusion with that of prophylactic transfusion in patient management.

Blood Pressure Measuring Devices

The recent widespread availability outside the medical environment of sphygmomanometers—devices to measure blood pressure—prompted a consensus development conference to develop language for proposed guidelines for the use and manufacture of the equipment. Over the past few years, coin-operated blood pressure measuring devices have been introduced in a growing number of public places, and take-home blood pressure kits have been on the market for some time. But as yet there have been no agreed-upon guidelines to cover the accuracy and lifespan of the sphygmomanometers or the recommended way to use them. In a move to fill this perceived gap in technology adoption, NHLBI brought together representatives of the medical profession, engineering, consumer groups, and government for the Consensus Development Conference on Improving Clinical and Consumer Use of Blood Pressure Measuring Devices.

During the conference, seven workshops addressed various aspects of proposed national voluntary guidelines and formulated recommendations for each of the following areas:

- Scope and labeling for automated and nonautomated sphygmomanometers;
- Performance requirements for automated and nonautomated devices;
- Test methods or validation procedures for automated and nonautomated sphygmomanometers;
- Special needs of patients such as children and the elderly.

Published recommendations will be made available to the public through the cooperation of groups that, with NHLBI, cosponsored the conference: the American College of Cardiology, American Heart Association, American Medical Association, Association for the Advancement of Medical Instrumentation, Food and Drug Administration, and the National Bureau of Standards.

Thrombolytic Therapy in Thrombosis

The most recent of the NHLBI-sponsored consensus development conferences, held in April 1980, addressed the problem of acute deep-vein thrombosis and pulmonary embolism.

For the last 30 years, the primary therapy used by nearly all physicians for management of these disorders has been anticoagulation. The technology under discussion in this conference was a newer therapy, administration of the thrombolytic agents urokinase and streptokinase.

Expert presentations and discussion questions dealt with the proven benefits of thrombolytic therapy, associated risks, patient selection, influences on current utilization, guidelines for patient management, economic aspects, and direction for future research. A consensus development panel, after examination of the above issues, prepared its statement. In essence, the panel concurred:

> "When properly used, in tandem with anticoagulation, thrombolytic therapy as currently practiced represents a significant advance in the management of proximal acute deep-vein thrombosis and the more severe forms of pulmonary embolism. With further developments aimed at improving its efficacy and reducing the bleeding risk, this form of therapy could become the initial treatment for all forms of acute deep-vein thrombosis and pulmonary embolism."

The Interagency Technical Committee: Coordinating the National Program

With a strong sense of need for cooperation on all fronts of biomedical research, the National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program coordinates all Federal activities related to the development and application of means to diagnose, prevent, treat, and control diseases of the heart, blood vessels, lungs, and blood. Indeed, this effort involves many disciplines and organizations and encompasses the full spectrum of activities related to biomedical research: basic and applied studies; clinical investigations and clinical trials; health services research and development; planning and development of health care services, facilities, and resources; health care delivery; and public and professional education.

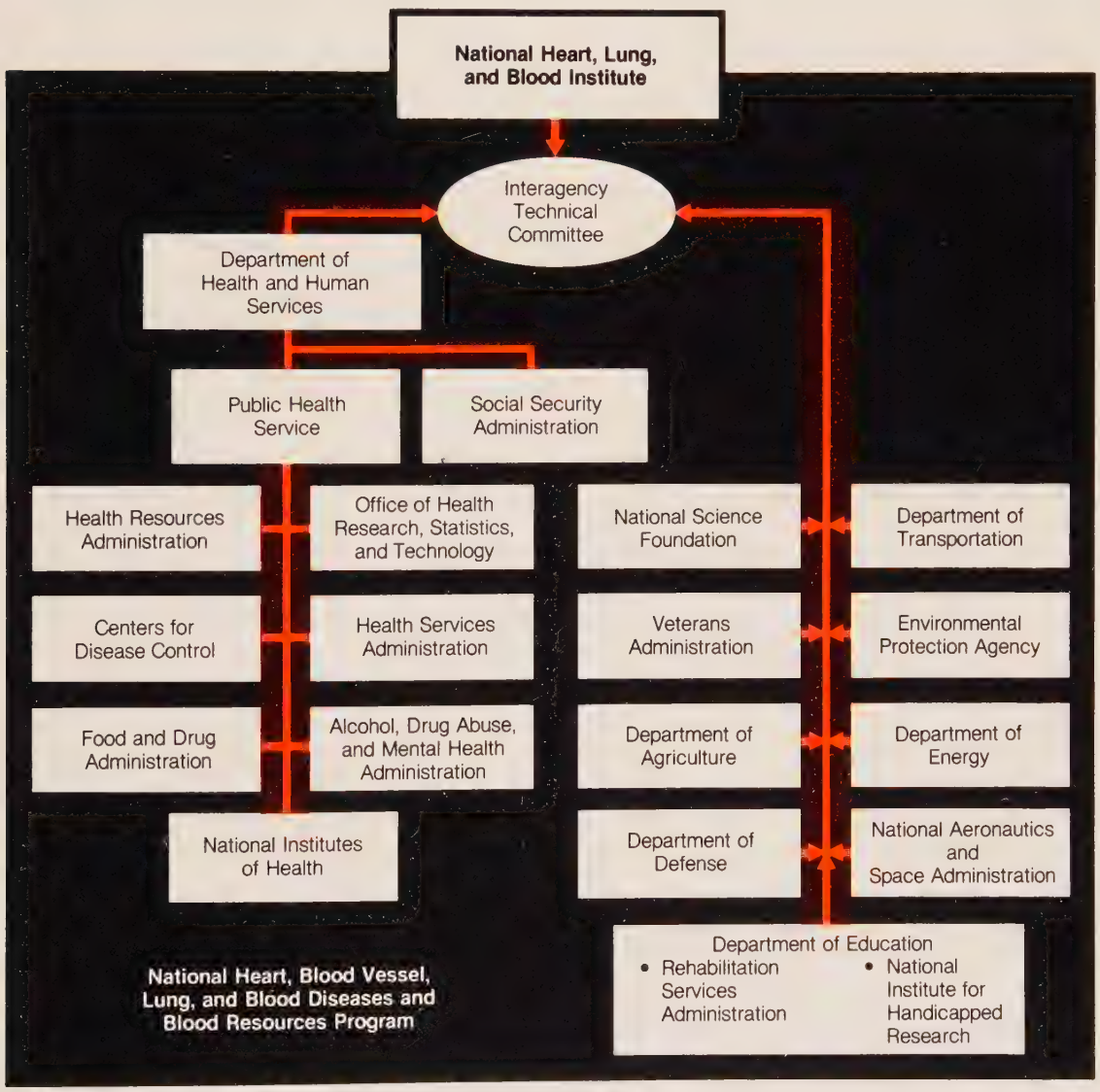
Organizations throughout the Federal Government conduct or sponsor activities related to the National Program. Their activities are combined with the efforts of private charitable organizations,

the industrial and financial sectors of the economy, and groups in private health care delivery settings. In providing leadership for the National Program, NHLBI has the responsibility to bring together the many insights, skills, and resources of these diverse groups to present a unified approach toward meeting Congressional and public mandates.

In view of the vastness and complexity of the National Program and the number of agencies involved in supporting related efforts, the Institute utilizes a range of formal and informal mechanisms for fostering National Program coordination. One of the most important of these formal mechanisms is the Congressionally mandated Interagency Technical Committee (IATC) on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources. Established in 1972, the IATC plays a crucial role through the collection and classification of program information, exchange of programmatic knowledge, provision of technical expertise, and promotion of collaboration among its member agencies. As shown in figure 10, 16 Federal organizations whose activities relate to the National Program participate in the IATC, with NHLBI in the role of lead agency.

As the foundation of IATC activities continues to be the exchange of information among scientists, clinicians, administrators, and other interested parties, the committee itself is mandated to report on all Federal activities related to heart, lung, and blood diseases. For 1977, the committee compiled and published the *Index of Federally Supported*

Figure 10.
Federal Agencies of the Interagency Technical Committee


National Heart, Lung, and Blood Institute
Interagency Technical Committee
Department of Health and Human Services
Public Health Service
Social Security Administration
Health Resources Administration
Office of Health Research, Statistics, and Technology
National Science Foundation
Department of Transportation
Centers for Disease Control
Health Services Administration
Veterans Administration
Environmental Protection Agency
Food and Drug Administration
Alcohol, Drug Abuse, and Mental Health Administration
Department of Agriculture
Department of Energy
National Institutes of Health
Department of Defense
National Aeronautics and Space Administration
Department of Education
• Rehabilitation Services Administration
• National Institute for Handicapped Research
National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program

Programs in Heart, Blood Vessel, Lung and Blood Disorders—FY77 and *Progress Through Coordination: The National Heart, Blood Vessel, Lung, and Blood Program.*

To determine the current scope of Federal activities related to the National Program, the IATC undertook a major activity during the past year in development of *National Program Coordination: 1979 Report of the Interagency Technical Committee on Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources.* The information in this report, as in earlier reports, is intended to allow Congress, the Administration, and participating agencies to identify areas that warrant greater emphasis, to delineate the roles of various agencies in support of the National Program, to minimize duplication of effort, to assess the overall impact of Federal efforts from multiple perspectives, and to facilitate overall program planning and coordination.

The first volume of the newly completed report describes the National Program, discusses the activities of the IATC, and presents a narrative summary of Program-related projects supported by the Federal Government in FY 1979, as reported to the IATC. All agencies that reported 10 projects or more in a given Program area have been included in the summary. The nature of each Program area is briefly described, as are the goals and objectives of each. Finally, descriptions of FY 1979 activities and some highlights of progress in each National Program area are presented. Volumes II and III provide a directory of detailed information on the majority of the research grants and contracts reported by the Federal agencies for FY 1979. The fourth volume of the report is the *Compendium of Federal Projects on Smoking and Heart, Lung, and Blood Diseases,* which provides an overview of Federal Government activities concerning smoking and heart, lung, and blood diseases and includes abstracts of more than 200 individual projects being supported by 16 Federal agencies in this research area. The nature and extent of participation by the National Institutes of Health and other major Federal organizations in the National Program are shown in tables 5 and 6.

Twelve components of the National Institutes of Health and 16 other agencies, including 10 within the Department of Health and Human Services, are involved in interagency projects relating to several areas of the National Program. The distribution of funding by major program area for the research activities being carried out by these Federal agencies, totaling more than $645 million, is shown in figure 11.

NHLBI provides the major portion of funding in all National Program areas. Other NIH Institutes are responsible for between 20 and 45 percent of the funding in all areas and other Federal agencies contribute approximately 20 percent of the funding in any of the three major program areas. Nearly 9,000 projects were federally supported, covering all of the major areas of the Program.

To strengthen the coordination and collaboration among Federal agencies concerned with various aspects of heart, blood vessel, lung, and blood disorders, particularly at the programmatic level, categorical working groups of the IATC have been established to address specific issues of importance to the overall Program. These working groups, shown in figure 12, are an important mechanism for focusing the combined expertise of various health-related Federal agencies on specific issues or areas of the Program and fostering the development of collaborative approaches to meeting specific Program objectives. The working groups, under direction of the IATC parent committee, plan and undertake or participate in specific projects of particular significance to the National Program. Highlights of IATC activities undertaken by these groups during the past year are discussed in the following paragraphs.

Parent Committee

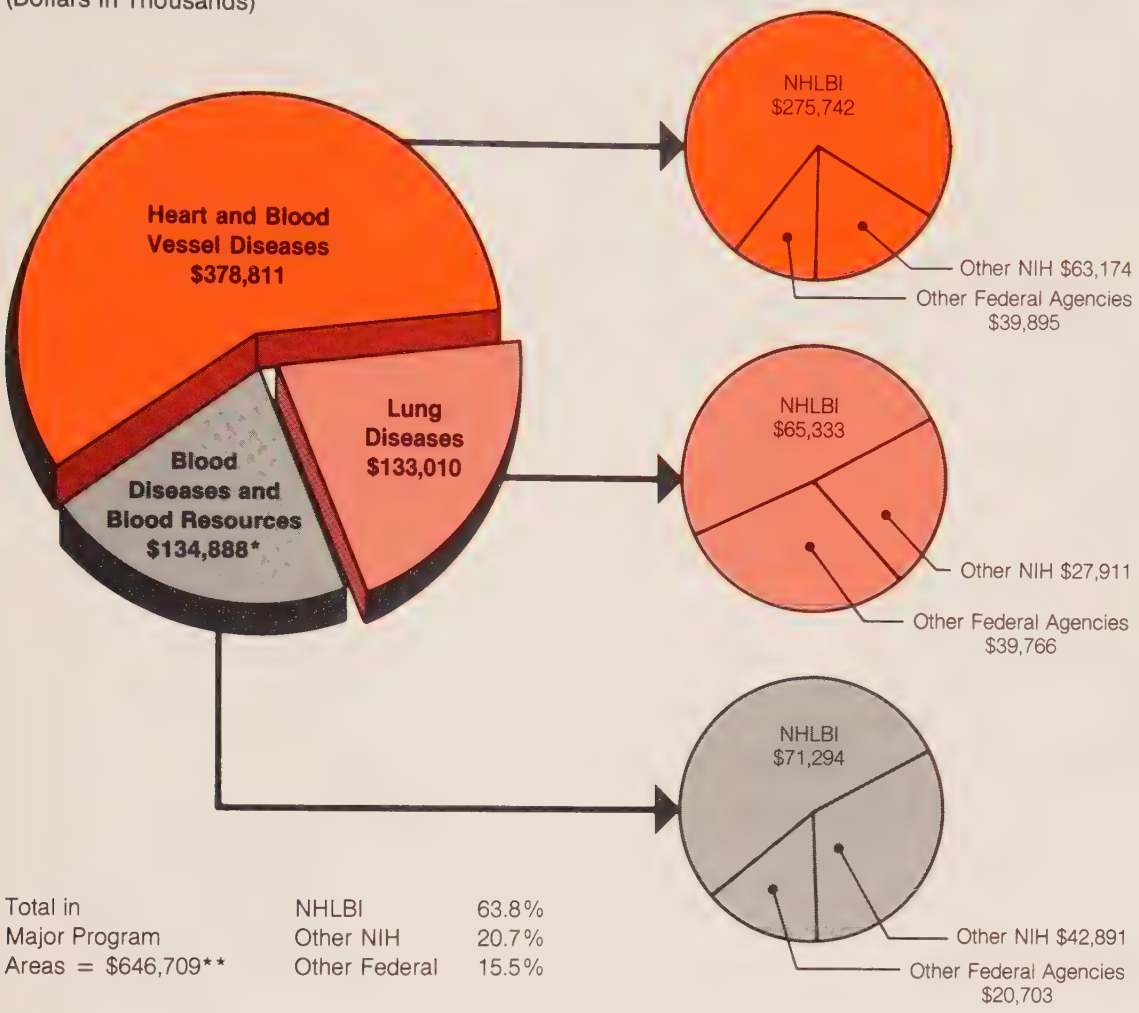
During 1978 and 1979, the parent committee discussed relationships among ongoing and planned activities, reported on organizational changes or changes in the members' relationship to the National Program, and reviewed activities and plans of the IATC categorical working groups. Key emphasis during recent meetings has included technology transfer, cardiovascular device development, and review of IATC working group activities.

In a recent parent committee meeting, NHLBI presented an overview of its concepts and approach to technology transfer, in the context of the Institute's role in biomedical research, assessment, and application. NHLBI emphasized that definition and development of assessment and transfer mechanisms is an ongoing process. To that end, NHLBI believes the IATC has a major participatory role in assessment and transfer of biomedical technology in all phases of the biomedical spectrum.

As a result, several IATC working groups are formulating new plans concerning clinical applications development. The parent committee is helping the working groups on several specific projects, including development and evaluation of smoking cessation programs, assessment of cardiovascular device technologies, and assessment of nutrition research findings.

In the development of cardiovascular devices, many agencies are involved in research, regulation, health care administration, and health care financing, making this issue an appropriate concern of the IATC. For example, the parent committee recently reviewed development of the left

Figure 11.
Distribution of Funding (FY 1979) Among Federal Agencies by Major Areas of the National Program
(Dollars in Thousands)



*Does not include any projects directly related to leukemias, blood cell formation, or the cellular immune system, but only those directly related to blood diseases and blood resources.

**Total does not include unavailable funding data indicated in tables.

ventricular assist device (LVAD) from two perspectives. NHLBI summarized its approach to clinical evaluation of the LVAD by presenting the historical perspective, technical description, clinical evaluation process, protocol development, patient selection criteria, and findings to date. At the same meeting, the Food and Drug Administration (FDA) discussed its role in development, regulation, and transfer of the devices. The discussion summarized the current status of FDA cardiovascular device classification regulations and noted four key areas for future interagency collaboration: identification of devices that can be improved by additional development, development of appropriate tests, differentiation of long- versus short-term safety factors, and determination of what safety and effectiveness data are needed.

Cardiovascular Biomedical Engineering Working Group

Efforts of the Cardiovascular Biomedical Engineering Working Group, with its emphasis on particular aspects and problems of device development and transfer, have formed a basis for parent committee discussions concerning technology transfer and assessment.

During the working group's most recent meeting, members focused on issues involved in development, assessment, and dissemination of several technologies. Areas identified by the group as appropriate interagency concerns include pacemakers, noninvasive diagnosis and evaluation

Table 5.
FY 1979 Federal Funding of Grants and Contracts by Major Areas of the National Program
(Dollars in Thousands; Does Not Include Amounts for Manpower or Training)

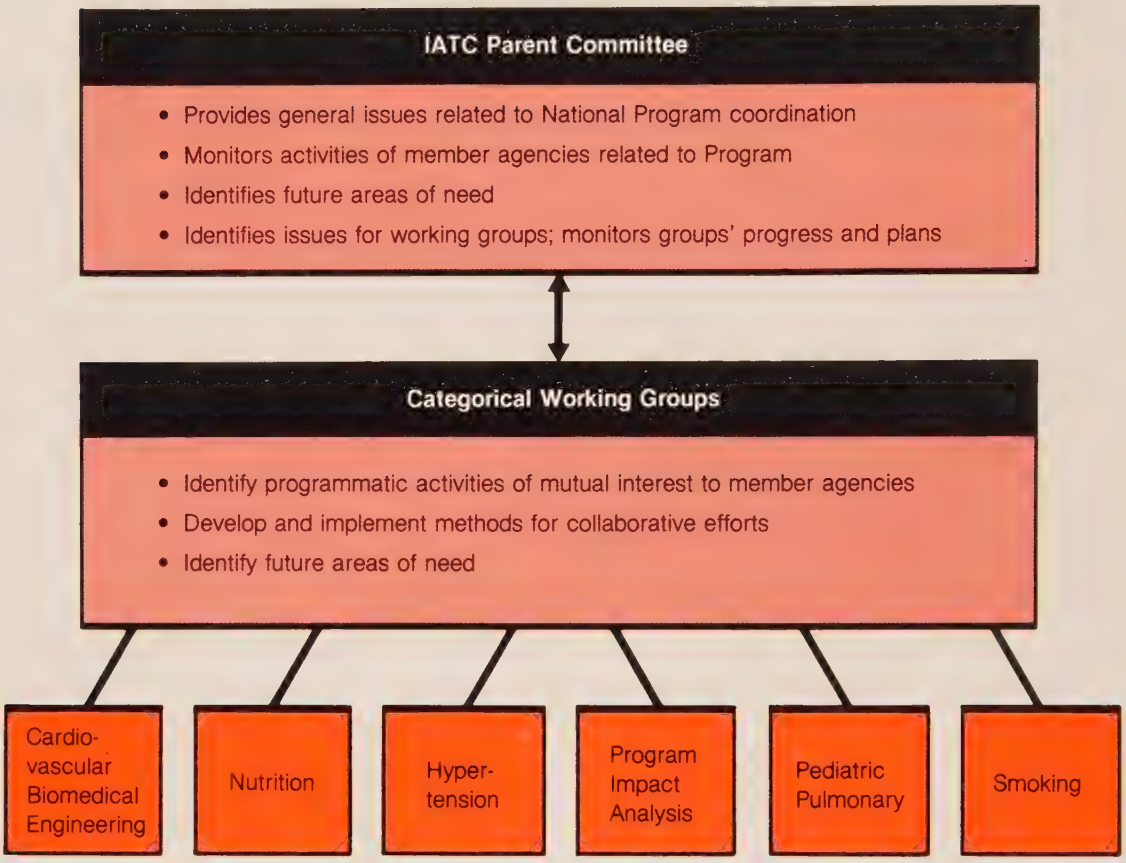
Federal Agencies	Major Program Areas			Total
	Heart and Blood Vessel Diseases	Lung Diseases	Blood Diseases and Blood Resources	
National Heart, Lung, and Blood Institute	$275,742	$ 65,333	$ 71,294	$412,369
Other NIH				
National Cancer Institute	758	799	18,094	19,651
National Eye Institute	15,520	422	—	15,942
National Institute of Allergy and Infectious Diseases	861	3,019	1,882	5,762
National Institute of Arthritis, Metabolism, and Digestive Diseases	7,953	1,228	9,103	18,284
National Institute of Child Health and Human Development	1,569	2,557	795	4,921
National Institute of Dental Research	281	—	241	522
National Institute of Environmental Health Sciences*	1,774	12,513	2,337	16,624
National Institute of General Medical Sciences	5,955	1,940	3,449	11,344
National Institute of Neurological and Communicative Disorders and Stroke	15,834	474	450	16,758
National Institute on Aging	909	49	—	958
Division of Research Resources	11,760	4,910	6,540	23,210
Total: Other NIH	$ 63,174	$ 27,911	$ 42,891	$133,976
Other Federal				
Alcohol, Drug Abuse, and Mental Health Administration	1,636	217	5,084	6,937
Center for Disease Control	261	1,288	—	1,549
Department of Agriculture	**	**	**	**
Department of Defense	3,809	4,994	3,485	12,288
Department of Energy	15,549	17,523	2,519	35,591
Department of Transportation	—	**	—	**
Environmental Protection Agency	781	4,644	526	5,951
Food and Drug Administration	296	—	1,426	1,722
Health Resources Administration	128	141	—	269
Health Services Administration	10,879	10,109	6,390	27,378
National Aeronautics and Space Administration	294	—	—	294
National Center for Health Services Research	3,785	—	—	3,785
National Science Foundation	1,127	500	1,272	2,900
Rehabilitation Services Administration/ National Institute for Handicapped Research	1,350	350	—	1,700
Veterans Administration	**	**	**	**
Total: Other Federal	$ 39,895	$ 39,766	$ 20,703	$100,364
TOTAL FEDERAL	$378,811	$133,010	$134,888	$646,709

* Includes intramural research projects.
** Data not reported.

Table 6.
Number of Research Projects Funded in Major Areas of the National Program, FY 1979

Federal Agencies	Major Program Areas			Total
	Heart and Blood Vessel Diseases	Lung Diseases	Blood Diseases and Blood Resources	
National Heart, Lung, and Blood Institute	2,434	434	526	3,394
Other NIH				
National Cancer Institute	14	13	138	165
National Eye Institute	148	1	0	149
National Institute of Allergy and Infectious Diseases	11	34	17	62
National Institute of Arthritis, Metabolism, and Digestive Diseases	101	18	110	229
National Institute of Child Health and Human Development	17	28	9	54
National Institute of Dental Research	3	0	4	7
National Institute of Environmental Health Sciences	22	145	23	190
National Institute of General Medical Sciences	101	26	55	182
National Institute of Neurological and Communicative Disorders and Stroke	91	5	5	101
National Institute on Aging	9	1	0	10
Division of Research Resources	1,052	480	713	2,245
Total: Other NIH	1,569	751	1,074	3,394
Other Federal				
Alcohol, Drug Abuse, and Mental Health Administration	20	4	32	56
Center for Disease Control	4	21	0	25
Department of Agriculture	70	21	26	117
Department of Defense	65	74	95	234
Department of Energy	25	72	14	111
Department of Transportation	0	1	0	1
Environmental Protection Agency	18	39	8	65
Food and Drug Administration	3	0	20	23
Health Resources Administration	2	1	0	3
Health Services Administration	57	24	43	124
National Aeronautics and Space Administration	6	0	0	6
National Center for Health Services Research	28	0	1	29
National Science Foundation	35	16	28	79
Rehabilitation Services Administration/ National Institute for Handicapped Research	7	2	0	9
Veterans Administration	749	237	211	1,197
Total: Other Federal	1,089	512	478	2,079
TOTAL FEDERAL	5,092	1,697	2,078	8,867

Figure 12.
Structure and Interrelationships of the Interagency Technical Committee


IATC Parent Committee
• Provides general issues related to National Program coordination
• Monitors activities of member agencies related to Program
• Identifies future areas of need
• Identifies issues for working groups; monitors groups' progress and plans
Categorical Working Groups
• Identify programmatic activities of mutual interest to member agencies
• Develop and implement methods for collaborative efforts
• Identify future areas of need
Cardio-vascular Biomedical Engineering
Nutrition
Hyper-tension
Program Impact Analysis
Pediatric Pulmonary
Smoking

methods, heart valves, and ambulatory monitoring. Additionally, the left ventricular assist device continues to be an area of interest.

Through the next series of meetings, the group will address these issues: establishing improved relations between Federal agencies and private research organizations; assessing patent rights in device development and the costs of device development and transfer; developing methods for collecting data on success or failure of devices; and encouraging device promulgation as appropriate. The working group is also considering involvement in preparing guidelines and standards for monitoring device development.

Working Group on Nutrient Composition of Foods

This IATC working group continued to focus on the development of a philosophy and mechanism for establishing cardiovascular priorities in the analysis of nutrient composition of foods. It recently included discussion of the Department of Agriculture's nutrient composition research program and how the working group can facilitate interagency collaboration in that area. In addition, the group continued its consideration of the data from two ongoing NHLBI studies: investigation of the relationship between nutrition and the presence of high density lipoproteins, and dietary intake findings from the Lipid Research Clinics prevalence study.

Working Group on Hypertension Control

Under the sponsorship of this working group, a conference on high blood pressure education and control for Federal employees was held. The results and recommendations are presented in a report, "Conference on High Blood Pressure Control in the Federal Work Setting." As a result of the conference recommendations, a number of activities have been initiated by Federal and other public agencies to develop and consider implementation of improved education programs in this important health area, particularly at the level of local health units. NHLBI is assisting in the development,

distribution, and promotion of materials. The Office of Personnel Management is now beginning a study of the effectiveness of the program.

The need for community resources to support employee health units was identified. Through the NHLBI, a directory of high blood pressure screening and education programs has been compiled.

Program Impact Analysis Working Group

In its role as facilitator of collaborative efforts within and among other IATC groups, the Program Impact Analysis Working Group has identified relevant data bases and sources extant in the Federal Government, identified data needs of member agencies, and discussed means for utilizing available data on cardiovascular and pulmonary diseases (including studies on trends in various risk factors). The working group has also considered approaches to assess what changes in risk factors and in patterns of care are associated with the continuing decline in coronary heart disease mortality. More recently, the working group has begun planning to assist in the 10-year update of the National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program Plan.

Pediatric Pulmonary Diseases Working Group

The membership of the Pediatric Pulmonary Diseases Working Group, which includes NHLBI, NIAMDD, NICHD, NIAID, and HSA, has been instrumental in joint program development. For example, over the past year the working group has provided input to the NIH Cystic Fibrosis Coordinating Committee on the development of a request for applications (RFA) for cystic fibrosis. Similarly, it has assisted NHLBI and NIAID in issuance of a joint program announcement on lung diseases and in sponsorship of a workshop on the treatment of asthma. Other recent activities have included assistance in developing plans for an impact evaluation of pediatric pulmonary disease research in the Lung Division of NHLBI, and initiation of plans for developing an in-depth index of federally supported research projects in pediatric pulmonary diseases. The group is presently considering whether this project should be continued.

Working Group on Smoking and Heart, Lung, and Blood Diseases

Since the first meeting of this newest IATC working group, in October 1979, members representing 16 Federal organizations have initiated a number of collaborative efforts related to smoking and heart, lung, and blood diseases. These efforts include:

- Smoking cessation education—The group has explored a variety of ways to approach the development and implementation of educational programs via the interagency mechanism. The group is serving as a review committee for an NHLBI-sponsored public media effort (under development) and is coordinating development of a pilot workshop on Federal physician education.
- Exchange of scientific information—The group has developed a compendium of Federal research projects related to smoking and heart, lung, and blood diseases. The compendium is volume IV of the current IATC overall report, and it will be updated periodically. In addition, the group has formed a biomedical/biochemical sciences subgroup to identify and exchange information on research issues and resources.
- Analysis of Federal policies on smoking—The Office of Personnel Management (OPM) has made available to the group a collection of Federal agency policies related to smoking/no-smoking areas in Federal facilities. NHLBI and other member agencies will continue to work with OPM to provide technical assistance in evaluation of these policies.

Through these and related means, the working group has periodically exchanged program information and encouraged interagency collaboration in the area of smoking and heart, lung, and blood diseases. Additional mechanisms will be developed as needed.

The working group will also cooperate actively with the NHLBI planning group on smoking and heart, lung, and blood diseases, both to share information and expertise concerning all Federal smoking programs and to make recommendations to the Institute for its research, education, and control efforts. Both groups will emphasize examination of existing smoking programs; assessment of their activities as they relate to heart, lung, and blood problems; identification of unmet needs; and indicating alternatives for future programs. Future programs may take the form of NHLBI initiatives or may be developed as cooperative endeavors between NHLBI and other Federal organizations that focus on smoking and heart, lung, and blood diseases.

NHLBI Research Programs: Collaborating Worldwide

Just as biomedical research knows no country, the burden of heart, lung, and blood disorders is not unique to the United States. Virtually all nations share, in varying degrees, the major health problems that NHLBI addresses.

For many years the Institute has been active in cooperative programs with scientists in other countries and with the World Health Organization (WHO). As the 1972 National Program has expanded the scope of research in this country, new opportunities for international projects have emerged. Concomitantly, the United States' success in lowering death rates from cardiovascular disease has prompted increased interest from the scientific and medical leadership of other countries. Through exchange of data with other nations, NHLBI can seek to accelerate toward achieving the much lower cardiovascular death rates of nations such as Japan, Italy, and Yugoslavia; at the same time, U.S. data may be of significant aid to developing countries that seek to deter the emergence of heart disease as a major economic and health problem.

More than 20 countries are involved in both formal and informal agreements with NHLBI; and the Institute funds a number of fellowships, contracts, and research grants to investigators worldwide. Exchange visits with researchers from other countries are an integral part of the international program activities. Some of the key activities of FY 1980 are described below.

Cardiovascular Disease Research With the U.S.S.R.

Since 1972, when a bilateral health agreement was signed by the U.S. Secretary of State and the U.S.S.R. Minister of Health, U.S. and Soviet scientists have collaborated in seven major research areas. An eighth was added in1974 under a separate agreement and both agreements were given a 5-year renewal in 1977. Currently under study are arteriosclerosis, ischemic heart disease, myocardial metabolism, congenital heart disease, sudden death, blood transfusion, hypertension, and artificial heart research and development.

Heart disease is the principal cause of death in both this country and the Soviet Union, so it is not surprising that public and scientific interest is intense in both countries, and that this program demonstrates a high level of information exchange and scientific activity. More than 100 institutions have participated in the joint health exchange, and since its inception 8 years ago, 480 specialists have been exchanged, 16 symposia have been held (with proceedings for 11 published and proceedings for the latest symposia in press), and more than 350 reports, abstracts, and related articles have been produced.

Lipid Research With Israel

This year saw the completion of a study of dyslipidemia in the Jewish population in Jerusalem; followup analysis will require an additional 2 years. Screening was conducted at the Jerusalem Lipid Research Clinic (established by NHLBI in 1975) and involved 17-year-old boys and girls reporting for physical examination prior to army induction. The location in Jerusalem provided a unique opportunity to study a multinational population—widely varied ethnic groups having significant differences in their heart disease rates, dietary patterns, education, and socioeconomic status. Over 15,000 persons have been screened, and preliminary analyses show important differences in lipid distribution and the intake of dietary fat in relation to country of origin. The study is also generating comparative data on the national diets of Israel and the United States.

Collaboration With Germany on Arteriosclerosis and Hypertension

The Agreement on Cooperation in the Fields of Biomedical Research and Technology, signed in 1976, emphasizes the linking of ongoing projects in the Federal Republic of Germany and the United States. Reciprocal visits by scientists and parallel data-gathering and processing have been cornerstones of the agreement. Cooperative activities have included the areas of epidemiological studies, education on smoking risk factor assessment, and high blood pressure education programs. A joint planning meeting was held in Germany in November 1980 to map out future cooperative activities.

Cooperative Activities With Italy

The Republic of Italy and the United States have worked cooperatively in the cardiovascular area since 1977. Delegations from the two countries have exchange-visited and met jointly to discuss the similarities and differences in national patterns of heart disease, cardiovascular risk factors, and approaches to controlling these problems. Lifestyle trends such as smoking and dietary habits have been compared in light of the two countries' cardiovascular mortality rates. A joint symposium, "Prostaglandins and Cardiovascular Disease," in November 1979 helped to direct future efforts to develop new priorities in the field of international risk factor assessment and control.

Polish Agreement on Cardiovascular Research

Joint symposia, exchange visits, and collaborative trials have all been part of the U.S.-Poland cooperative agreement begun in 1974. In December 1979, a working group from this country visited Poland for a joint symposium on cardiovascular

diseases. The meeting was part of the agreement to continue joint activities in the areas of epidemiology of cardiovascular disease, cardiovascular disease rehabilitation, etiology and pathogenesis of atherosclerosis and hypertension, and noninvasive methods for assessment of cardiac function. Polish scientists also are participating in the ongoing European Collaborative Trial in Multifactorial Prevention of Coronary Heart Disease. The goal of 10,000 screening examinations includes 9,000 workers in factories designated for intervention and 1,000 in factories selected as controls (no intervention). Risk factors chosen for intervention include hypercholesterolemia, overweight, hypertension, smoking, and lack of physical activity.

Coronary Heart Disease Respiratory Studies in Yugoslavia

Since 1973, Yugoslavia and the United States have worked cooperatively on projects of mutual interest. The epidemiology of cardiovascular disease has been a primary topic under the agreement. The incidence of coronary heart disease among the 11,000 Yugoslav men in a long-range followup study is about one-fourth the incidence in the U.S. Framingham study. However, repeat measurements of blood pressure at regular intervals indicate that the prevalence of high blood pressure among Yugoslav men is increasing. Data analysis continues for a respiratory study in which 3,000 persons have been screened for a genetic defect that causes an enzyme deficiency leading to development of severe familial emphysema.

Cooperation With Other Countries

Formal and informal agreements for collaborative activities with other nations include:

- **Great Britain**—continuing development of a computer-based chemical information system;
- **People's Republic of China**—start-up of exchange visits and development of plans for future cooperation in cardiovascular research.
- **Japan**—comparative studies of coronary heart disease rates and variations in genetic, nutritional, environmental, and other factors.

In addition, the Institute continues cooperative activities with many other countries and multinational organizations such as the World Health Organization and the Pan American Health Organization. Proposals are pending for future NHLBI cooperation with several additional countries, particularly in the developing areas of the world.

Training and Manpower Development: Preparing Tomorrow's Scientists

Clearly, the continued strength of biomedical research in the United States is dependent on the renewal of the human resources which make it possible. However, intensified competition for limited financial resources at all levels of government has led to the concept of "stabilizing" the base of biomedical research project grants, even if it means a reduction in the training of the next generation of basic and clinical investigators. Simple logic provides that without research, all scientific exploration must cease, but research training itself is the key to accomplishment. A number of recent studies have spotlighted the dramatic decline of physicians entering careers in academic investigative medicine. The NHLBI views this as a problem of critical importance to the continued progress of medical knowledge and, in particular, our recent and future accomplishments in cardiovascular medicine.

In 1980, the NHLBI supported a total of 1,549 trainees pursuing research related to the diagnosis, prevention, and treatment of heart, lung, and blood diseases, the use of blood and blood products, and the management of blood resources. While this is an excellent continuation of ongoing efforts, there are many special needs and demands resulting from social trends, the growth of NHLBI mandates, and expanding areas of investigation. Particularly, as these fields of study have become increasingly sophisticated, educational programs are critical to assuring a sufficient number of dedicated professionals knowledgeable in the most up-to-date methods of investigation and clinical application. In spite of these needs, there has been little growth in the numbers of trainees since 1972 when there were 1,369 trainees and a much more narrow scope of Institute responsibility.

Of particular concern to the NHLBI is the alarming decrease in personnel training in the cardiovascular field. This decrease—about 50 percent since 1970—is partially masked by increased numbers of trainees in the lung and blood areas, the mandates for which were added to the Institute in 1972. Continuation of this downward trend will mean fewer trained scientists and clinicians performing cardiovascular research at a time when the potential for making significant progress toward the prevention of heart and blood vessel diseases and the efffective control of their complications is so great.

Similar downward trends are reflected in a history of cardiovascular research career recipients. In 1970, 143 investigators received research career development appointments. However, in 1979,

despite three additional mechanisms available, only 130 investigators are receiving career development awards. The total increase for the NHLBI is made possible only by the innovative career development programs in the lung area and a steady state of career development appointees in the blood area.

A special problem is the dearth of physician investigators in the cardiovascular training program. While there were 601 medical doctors in the 1970 training programs, there were only 214 in the 1978 programs. This number increased slightly in 1979, but the problem remains an important one.

Programs and Awards

The Institute's manpower programs can be considered in four distinct but interrelated categories:

- Programs dealing strictly with the training of individuals. These are grouped in the National Research Service Awards (NRSA) and include training grants, fellowships, and certain minority training programs. In addition to supporting postdoctoral fellows in specified areas of cardiovascular biomedical and behavioral research where a documented need for trained manpower exists, the NRSA mechanism also supports institutions to develop or enhance research training opportunities.
- Programs to bridge the transition between training and research for new investigators. The New Investigator Research Award and the newly established Clinical Investigator Award programs, for example, are designed to encourage new investigators (including those who have interrupted early promising research careers) and recently trained physicians to develop their basic and clinical research interests and capabilities in heart, lung, or blood disease areas.
- Programs for research career development for both clinicians and academic investigators. Research Career Development Awards are available for those with doctorates in either the clinical or nonclinical sciences whose research potential is apparent but who need further experience in the development of independent research careers.
- Programs for special needs such as curriculum development or specialty manpower shortages. The Preventive Cardiology Academic Award, for example, was initiated in 1979 to provide a stimulus for the development of a preventive cardiology curriculum in those schools of medicine and osteopathy that do not have one and to strengthen and improve the preventive cardiology curriculum in those schools that do.

Within the constraints imposed by limited resources, each of the three divisions of heart, lung, and blood diseases has made significant educational accomplishments during the past year. The paragraphs that follow discuss these accomplishments in light of the special problems in each area of investigation.

Division of Heart and Vascular Diseases

The Division of Heart and Vascular Diseases currently supports 552 postdoctoral and 237 predoctoral training positions. However, this total of 789 trainees is only about 75 percent of that supported in 1972 and 33 percent of the number estimated as necessary to meet the needs projected by the National Heart, Blood Vessel, Lung and Blood Act of 1972. All program areas need specially trained independent investigators. Cardiomyopathies and infections of the heart have particular shortages of investigators, and there is a special need for academic physicians, epidemiologists, nutritionists, behavioral scientists, and geneticists in cardiovascular areas. Despite the fact that the level of support remains close to that of 1972, even in the previous year it was noted that there were 223 unfilled cardiovascular faculty vacancies in medicine, pediatrics, and surgery departments of 96 major medical schools. The National Research Council's *1978 Report on Personnel Needs and Training for Biomedical and Behavioral Research* stated that budgeted faculty vacancies for clinical departments in medical schools had decreased 11 percent per year since 1972, and basic science departments reported an average increase in vacancies of 4 percent per year. In addition, a number of special shortage areas have been identified. These include:

- Behavioral science
- Basic investigations of tissue metabolism and regional blood control under conditions of ischemia
- Cardiovascular biomedical emergency
- Population genetics
- Study of lipoprotein metabolism
- Endocrinology as it relates to the cardiovascular complications of diabetes
- Specialized study of coagulation in heart disease and stroke
- Nutrition
- Epidemiology
- Biostatistics
- Hypertension control
- Adult and pediatric cardiology.

In attempting to meet these pressing needs, the Division of Heart and Vascular Diseases has continued its efforts and made modest expansions in some new areas.

National Research Service Awards have supported 237 predoctoral and 175 postdoctoral trainees during FY 1980.

The *Minority Hypertension Research Development Summer Program* has supported 40 graduate students and 93 faculty members of minority institutions.

Short-Term Training for Students in Health Professional Schools is a new program which has attracted 12 applications, with a significant cardiovascular component allowing support of 238 students.

The *Continuing Education Program in Cardiovascular Epidemiology* has sponsored a fifth annual workshop, bringing the total number of graduates to 100.

The *Research Career Development Award Program* is now funding about 20 new competing awards each year and providing continued support for about 80 previously approved applications.

The *Special Emphasis Research Career Award in Diabetes Mellitus, DHVD,* has supported seven FY 1980 awards, two of which were new awards.

The *Preventive Cardiology Academic Award Program* has made 10 recent awards.

The *Clinical Investigator Award Program* has made 17 awards in FY 1980, and the intense interest expressed suggests that this program will have continuing success in increasing the pool of physician investigators.

The *Minority Biomedical Support* in which DHVD participates has made 23 awards supporting 120 students.

The *Minority Access to Research Careers Program* has supported five fellowships for cardiovascular research training in FY 1980.

Division of Lung Diseases

Over an 8-year period, the number of postdoctoral trainees supported by the Division of Lung Diseases has increased 128 percent; the number of M.D.'s receiving training has doubled; and the number of Ph.D.'s has tripled. Despite these successes, the proportion of physician investigators continues to decline, creating a strongly felt need. In addition, the Division recognizes a need to increase investigator supply in special areas such as epidemiology, behavioral medicine, mucous biology, lung cell biology, membrane transport, and pediatric pulmonary disease.

In its efforts to meet these needs, the Division of Lung Diseases has continued its ongoing programs and expanded activities in some new areas.

The *Research Career Development Awards Program* currently includes 32 awards, 6 of which were initiated in FY 1980. Community interest in this program appears to be mounting, as indicated by an increase from 3 approved applications in 1978 to 13 approved applications in 1980.

The *Research Career Award Program* supports seven senior investigators, all of whom are nearing their 20th year of funding.

The *Pulmonary Academic Award Program* initiated 6 new awards in FY 1980, and a total of 62 medical schools have held awards at some time in the past 10 years. A special program evaluation will be conducted during 1981 to assess program impact.

The *Medical School Pulmonary Faculty Training Award Program* conferred six new awards in FY 1980.

The *Clinical Investigator Award Program* made 14 awards in pulmonary areas during FY 1980.

The *Minority Biomedical Support Program* has awarded three projects in pulmonary areas. These are intended to strengthen the institutional research and research training capabilities of 4-year colleges, universities, and health professions schools whose students are mainly from ethnic minority groups.

Division of Blood Diseases and Resources

There are continuing needs for research training in a number of specialty areas, notably blood transfusion sciences, thrombosis and hemostasis, and red cell studies and red cell disorders including sickle cell disease and thalassemia. It is estimated that a minimum of 180 fellows per year are needed in all the high-priority areas cited above. Particular emphasis is placed on providing training in blood transfusion sciences since this is a rapidly expanding and increasingly complex area. In FY 1980, the Division supported 190 fellows, 18 of which were new awards. Two major program mechanisms have been used to continue activities and modestly expand training efforts.

The *National Research Service Award Program* encourages submission of applications in all of the high-priority areas identified by the Blood Diseases and Resources Advisory Committee. A special program announcement yielded 23 new awards in FY 1980 for a total of 44 postdoctoral fellows. Thirty-one fellowships are conducting research in thrombosis and hemostasis problems, six in red blood cell diseases, six in sickle cell diseases, and one in blood transfusion sciences.

The *Institutional National Research Service Award Program* has added 14 new awards in FY 1980, increasing the number of DBDR-supported grants to 36 for 137 trainees. Training programs in blood transfusion sciences have been given particular encouragement because large numbers of trained professionals are needed to fill vacancies in regional blood banking centers.

Prospects for the Future

Over the past decade, the NHLBI has reaffirmed its commitment to the timely training, education,

and career development of scientists and clinicians engaged in biomedical research. The Institute believes that no cardiovascular, pulmonary, or blood disease problem is so complicated that it cannot be attacked, understood, and ultimately remedied. The need for an adequate manpower base for this scientific enterprise is clear. As Richard S. Ross, M.D., illuminated at the 52nd Annual Scientific Sessions of the American Heart Association:

> "Bright people are required in large numbers because the process of scientific discovery is, by its very nature, inefficient. Many blind alleys must be explored for each road which leads to an important therapeutic development....
>
> "Another reason that the number of investigators must be large is that it is impossible to identify creative scientists with certainty before they have had an opportunity to try science... This means that the number of young people who start on research careers must be far greater than the number who become productive scientists."

It is not clear, however, that this need will be met if the decline in physician researchers continues. During the last 10 years, a number of professional societies have identified specific requirements including behavioral scientists; chemists and investigators with specialized training in endocrinology and metabolism; experts on blood coagulation; blood banking personnel; individuals with expertise in fundamental nutrition, lipid metabolism, growth and development, and pediatrics; and epidemiologists and biostatisticians. Currently, there is an exceptional need for nutritionists and epidemiologists to fill vacancies in important new programs which have evolved in response to the 1972 National Heart, Blood Vessel, Lung and Blood Act. These include the centers programs, clinical trials programs, and prevention, education, and control programs.

Some individuals have advanced the theory that government should provide better monetary incentives for physicians entering academic careers. Suggestions include reexamination of Federal policies prohibiting stipend support for M.D.'s attaining their professional degree, eliminating payback provisions on NRSA stipends, increasing stipends, and ensuring stability of the scientific research base.

In the Institute's view, the changing scene for pursuing academic research and training presents a challenge not only to government, but to the academic biomedical community as well. This challenge can be viewed as an opportunity for the biomedical community to present its needs and requirements, to work with all branches of the Federal Government, with lay groups, and with the National Research Council of the National Academy of Sciences, as the means of providing continuing and realistic assessments of manpower needs to the Nation. Only through such cooperative efforts will we be able to ensure an adequate influx of capable clinical investigators—individuals who can bring clinical insights to bear on basic research results, who can maintain the obvious link between the laboratory and the clinic, and who will be the teachers of the next generation of researchers.

Specialized Centers of Research: Teaming To Combat Diseases

To foster effective "critical masses" of investigators working on problems of mutual concern in heart, lung, and blood diseases, NHLBI has developed Specialized Centers of Research to study nine problems of unusually large impact: arteriosclerosis, hypertension, ischemic heart disease, chronic airways disease, pediatric pulmonary disease, pulmonary vascular disease, fibrotic and immunologic interstitial lung disease, adult respiratory failure, and thrombosis. The 44 NHLBI-supported SCOR's across the country provide a planned, coordinated national program of basic and clinical research directed toward the diagnosis, treatment, and prevention of these specific diseases.

A SCOR is an organizational unit located within a larger institution, drawing together a variety of research projects related by a central theme. Each SCOR must meet rigid requirements that distinguish it from regular project grants and enhance the focusing of resources, clinical trained manpower, and scientific knowledge.

Each SCOR involves a group of established investigators in both basic and clinical sciences with an interest in a particular disease or group of diseases. The scientists have access to sophisticated facilities for clinical investigations and an appropriate complement of patients for study and long-term followup. Included in the SCOR are research laboratories and pathology, data management, biostatistical, and other types of support needed to study the targeted disease.

In addition to resources the SCOR provides an organizational structure to enhance scientific communication. Within the individual SCOR, investigators have opportunities for collaboration both with scientists working in the SCOR and with scientists working in related areas within the host institution. Moreover, each SCOR participates in a continuous process of assessment and interaction internally and with other related SCOR's.

Some of the recent scientific accomplishments of the SCOR program, now in its ninth year, are summarized in the following paragraphs.

Hypertension SCOR's

NHLBI supports five SCOR's that emphasize research in hypertension. Examples of accomplishments during the past year are given below.

- The majority of patients who have severe or malignant hypertension are found to have extremely high renin levels. For many years the treatment of such hypertensive emergencies has posed a considerable challenge to physicians in clinical practice. However, drugs are now available which specifically block renin release or inhibit angiotensin II formation. In a recent study of one such drug, captopril, blood pressure was lowered almost immediately and significant clinical improvement was noted within 1 hour of administration. Captopril appears to be a uniquely effective treatment for malignant phase hypertension and, because of its rapid onset of action, it may be used in selected cases of malignant hypertension instead of more risky intravenous therapies.

- To test the hypothesis that abnormally high and abnormally low levels of renin seen in essential hypertension reflect differences in sympathetic nervous activity, plasma renin, norepinephrine, and epinephrine were measured in a group of patients before and during a 30-minute period of head-up tilting. During tilting, norepinephrine and epinephrine levels rose in all patients, but there were no differences between the groups, despite major differences in the renin responses. The most striking difference between groups was that 40 percent of the high-renin patients fainted during tilting, while none of the low-renin patients did. Therefore, to the extent that plasma catecholamine levels reflect sympathetic nervous activity, the data indicate that the differences in renin levels between the groups cannot be attributed to differences in neural activity, but could reflect different levels of responsiveness. The high incidence of fainting in the high-renin patients is compatible with the view that they have a relative deficiency of blood volume when compared to low-renin patients.

- Studies have continued on the use of angiotensin converting enzyme inhibitors in the treatment of congestive heart failure and hypertension. Recent work has demonstrated that inhibition of converting enzyme with teprotide has an almost immediate beneficial effect in heart failure by reducing peripheral vascular resistance and increasing cardiac output. Preliminary studies with captopril have suggested similar effects. Inhibition of angiotensin converting enzyme continues to be one of the most promising developments in the treatment of refractory hypertension and congestive heart failure.

- Important new observations have been made on the effect of hypertension on the arterial endothelium of rats. Even after a relatively brief period of hypertension, increases in cell number and cell shape have been shown. These findings are also associated with areas of endothelial injury as well as irregularities in the cell nuclei. The data demonstrate that hypertension may have a major effect on endothelial structure and function.

- Recent research suggests that blood pressure determination alone may not be a sufficiently precise indicator of the risk of subsequently developing cardiovascular disease. Many hypertensives sustain elevated blood pressure for years, despite therapeutic intervention, without developing serious disease. These data support the contention that hypertension is a heterogeneous disease and more sophisticated means are needed to categorize the hypertensive population in order to refine prognosis, assign therapy, and perform clinical research with greater precision. With more sensitive and precise methodology, investigators can differentiate those hypertensives in need of intensive therapy from those who are not at great risk of developing cardiovascular disease and in whom therapy is unlikely to alter hypertension.

Arteriosclerosis SCOR's

Current activities of the eight Arteriosclerosis SCOR's supported by NHLBI center on study of hyperlipidemia and vascular disease. In addition to clinical research they include animal and tissue studies and basic laboratory investigation. In the past year, several noteworthy advances have occurred:

- One of the most hopeful developments of the past few years has been the hypothesis that atherosclerosis may be made to regress by controlling dietary cholesterol levels or by drug therapy to reduce plasma cholesterol levels. An evaluation of the progression and regression of coronary artery atherosclerosis in 129 rhesus monkeys over a period of 5-1/2 years has recently been completed. The monkeys were maintained for 19 months on an atherogenic diet which raised mean plasma cholesterol to 793 mg/dl and were then segregated into four groups on diets which maintained cholesterol levels at 200 or 300 mg/dl for 24 to 48 months. The design of the regression phase was to simulate cholesterol reduction to levels equivalent to those of individuals with modest hypercholesterolemia (300 mg/dl) or to levels which might be attained in these individuals (200 mg/dl) by more successful diet or drug therapy. Quantitative morphometric methods were employed to differentiate actual changes in the arterial lesions (progression or regression) from changes in the artery associated with growth. The results indicate no coronary artery regression occurred at 300 mg/dl and that the rate of coronary artery plaque regression at 200 mg/dl was between 0.54 percent and 0.65 percent per month. Data are now being collected from a similar 7-year study in which the duration of atherogenic diet is 38 months.

- For some time it has been suspected that nutritional influences in infancy and youth may play a role in subsequent development of atherosclerosis. A recent study has tested the effects of differing levels of dietary cholesterol or serum cholesterol levels in infant baboons. To determine the effects of infant diet on serum cholesterol levels, 96 infant baboons were breast-fed or formula-fed diets with 2, 30, or 60 mg/dl cholesterol and subsequently weaned on one of four long-term diets with two types of fat and two levels of cholesterol. No significant effects on serum cholesterol have been observed after 3 years. The study does continue to demonstrate, however, the striking genetic influence of the sire of the matings on the subsequent cholesterol level of the progeny.
- Smoking is known to be one of the risk factors for coronary heart disease and it has been suspected that smoking plays a role in the development of atherosclerosis. However, recent studies in animals have failed to demonstrate an effect of smoking on atherogenesis. Autopsy results from a 3-1/2 year study of cigarette smoking baboons have shown no statistically significant difference in the degree of arteriosclerosis among 30 male, diet-induced hyperlipidemic baboons smoking cigarettes and those puffing on sham cigarettes. Interpretations to be applied for the redesign of the cigarette-smoking baboon model are that the level of serum cholesterol attained was too low to provide a rate for the atherosclerotic disease progress which would be susceptible to augmentation by smoking; and that the observed higher blood carbon monoxide and thiocyanate levels, and the urinary cotinine concentrations, in smoking animals reflect less than the maximal degree of cigarette inhalation required for augmentation of arteriosclerosis.
- It has been observed that the level of serum cholesterol in children decreases during puberty. In an extension of these observations, recent studies have examined low density lipoprotein levels. In white male youths it has been observed that the ratio of LDL to high density lipoprotein rises dramatically during adolescence. The change in the ratio (1.2 to 1.65) between the ages of 11 and 17 reflects an early increase of LDL cholesterol and an inordinate drop of HDL cholesterol. However this change has *not* been observed in black males or in females of either race.
- The development of ^{14}C-sucrose conjugate with low density lipoprotein and the demonstration that tissue lysosomes take up the conjugate, degrade the LDL component, and entrap the metabolically inert sugar has provided a striking new tool for *in vivo* and *in vitro* quantification of the uptake and utilization of LDL by tissues. ^{14}C-sucrose accumulation in lysosymes serves as a marker for LDL and its concentration is a directly proportional measure of the number of LDL molecules degraded by the tissue. The method has been applied to determine the tissue sites of LDL degradation in swine. Tissues included all organs, muscle and adipose tissue, digestive tract, and all remaining tissues excluding bone. Approximately 40 percent of the LDL was degraded by the liver. Expressed as uptake relative to wet weight of tissue, the adrenal and the ovary were the most active tissues. The relative ranking of the adrenal and ovary presumably reflect their utilization of cholesterol for the synthesis of hormones.
- A pilot total-family lipid intervention study has been conducted to compare the effects on lipid reduction in children, of detailed diet instructions to the family by a nutritionist, versus routine care of the family by a physician. The study was initiated from evidence that one-third of 83 progeny of 33 young myocardial victims (before age 50) had cholesterol levels above the 90th percentile of an age/sex matched reference group. Results of randomization of the families into diet instruction (16) and physician care (17) showed that, after 10 months, a significant lowering of total plasma cholesterol and low density lipoprotein occurred only in the progeny of the instruction group.

Ischemic Heart Disease SCOR's

At the eight NHLBI-supported Ischemic Heart Disease SCOR's, research is directed at a variety of issues such as protecting heart tissue during periods of decreased oxygen supply, measuring the extent of heart muscle damage, and testing methods to treat angina pectoris. Some of the scientific accomplishments made in the past year are summarized below.

- Progress has been made in developing a computerized mapping system for the propagation of arrhythmias of the heart. By this method, certain patient characteristics of dysrhythmia are scored and this provides a good prognostic index. In the past year investigators have succeeded in recording an extremely rapid polymorphous ventricular arrhythmia. It was possible to replay the recording and demonstrate the feasibility of reconstructing the complex ventricular dysrhythmia on a beat-by-beat basis. This achievement demonstrates the use of computerized mapping systems and their potential for investigations of the mechanisms responsible for initiation and perpetuation of ventricular dysrhythmia associated with myocardial infarction.
- A recent prospective study has developed methods to successfully identify patients with myocardial infarction who are hemodynamically

stable but are at high risk of death following hospitalization. It has been possible to identify a number of variables that predict the persistence of angina pectoris, recurrent myocardial infarction, and early cardiac death. These variables include number of obstructed vessels, reduced ejection fraction, heart failure, history of prior infarction, late-hospital ventricular arrhythmias, and other factors. By use of an objective computerized scoring system and using two variables, it has been possible to identify patients who have a very high risk of dying but who are, at this stage, hemodynamically stable. The investigators will now concentrate efforts on developing an intervention trial to prevent recurrence of myocardial infarction in these patients.

- During this last year, some preliminary results have indicated a promising new technique to quantify infarct size. Antibody Fab (fragment, antigen-binding) fragments, labeled with radionuclides, strikingly concentrate in zones of infarction, whereas nonspecific immunoglobulin fragments do not accumulate. Extensive documentation of this finding has been obtained using dogs. New methods have been devised for labeling actomyosin antibody fragments with a variety of radionuclides utilizing the covalent attachment of a chelating agent to the antibody Fab fragment. ^{66}Gallium-labeled myosin specific antibody Fab fragments have been utilized to image myocardial infarcts with the positron camera. ^{111}Indium and ^{99m}technetium images have been produced with a gamma camera after these radionuclides were linked to antibody. Very early images were demonstrated with the technetium-labeled Fab fragment. The short half-life of this radionuclide and the relatively small radiation dose delivered indicates that human studies may soon be feasible.

Chronic Airways Disease SCOR's

Three specialized centers supported by NHLBI are directed at problems associated with conduct of basic, applied, and clinical research projects for chronic airways disease such as emphysema, chronic bronchitis, and asthma. Examples of recent accomplishments are presented below.

- Characterization of individuals at risk for the development of airways obstruction is one of the major goals of the SCOR program. If these individuals can be identified at an early age, it may be possible to modify factors that contribute to that risk. A number of risk factors associated with airways obstruction have been defined, and in the last year a comparison of their relative importance and contribution to subsequent disease development has been undertaken. In order of importance, the factors were: (1) age—subjects older than 45 had higher rates of abnormality; (2) smoking—smokers had 3 times the disease rate of nonsmokers; (3) socioeconomic status—subjects from the lowest socioeconomic groups had significantly more disease than those from higher socioeconomic groups; (4) family history—first-degree relatives of patients with obstructive lung disease had higher rates of abnormality; (5) sex—males had higher incidence of disease than females; and (6) secretor status—nonsecretors of ABH antigens had more disease than secretors had. On the basis of these results, investigators should be able to predict the risks of developing obstructive airways disease with greater certainty.
- Exposure of dogs to high levels of sulfur dioxide gas for extended periods results in airway lesions with anatomic characteristics similar to those observed in human bronchitis. However, in human subjects it has not been clearly established whether the airway changes of chronic bronchitis are associated with alterations in airway responsiveness to inhaled bronchoconstrictors. To address this question, the effects on airway responsiveness of repeated exposure of dogs to sulfur dioxide was examined. After 6 months of exposure at a dose level of 150 parts per million, all four animals became significantly less responsive to aerosol histamine (a bronchoconstrictor) challenge. Following removal from sulfur dioxide exposure for 8 weeks, the animals returned to their initial level of histamine responsiveness. Based on these preliminary results, it appears possible that airway irritation with sulfur dioxide may trigger a series of physiological changes which act to protect animals from further airway insults.

Adult Respiratory Failure SCOR's

Three SCOR's are supported by NHLBI to conduct studies on biochemical, immunologic, and physiologic mechanisms of acute lung injury and repair in order to improve the diagnosis, management, and prevention of adult respiratory distress syndrome. Some recent advances are:

- Available evidence indicates that collagen, the tough protein that tendons are made of, is produced in greatly excessive amounts following some types of lung injury. Accumulation of this protein renders the lung inelastic and nondistensible, seriously altering its function. However, there are many types of collagen which differ in important ways, including their susceptibility to break down by various compounds. It is important, therefore, to fully characterize the types of collagen that accumulate in the lung after an injury so that effective forms of treatment can be devised.

  During this past year, experimental models of lung fibrosis in animals have been developed

through the use of chemical agents that produce acute lung injury. Analysis of the connective tissues in the lungs of humans who died of acute respiratory failure has also been undertaken. Most importantly, a new technique for the extraction of collagen from these lungs has been developed. Up to now, only about 15 percent of the lung's collagen could be removed for biochemical studies because it is so resistant to degradation and that which is removed may not be representative of all lung collagen. With the new technique, researchers have been able to remove 60 percent of the collagen. This advance will greatly facilitate the analysis of the types of collagen present, as nearly all of the protein present will be studied, and comparisons of the relative collagen constituents in normal and abnormal lungs can be made.

- It has recently been demonstrated that a reliable "profile" of the status of surface phospholipids in the lung can be obtained from lung washings. These materials, called surfactant, are responsible for preventing collapse of the air spaces (alveoli) in the lung, a characteristic finding in acute respiratory distress syndrome (ARDS). Furthermore, the studies to date suggest that the structure of surfactant is abnormal in ARDS and returns toward normal as the patient recovers. Interestingly, the abnormalities in these adults resemble those previously noted in infants with respiratory distress syndrome. This suggests that adults with ARDS develop an "immature" lung due to loss and regeneration of the cells responsible for surfactant production.

Pulmonary Vascular Disease SCOR's

NHLBI supports three specialized centers in pulmonary vascular diseases which focus on basic and clinical research in pulmonary hypertension, cor pulmonale, and pulmonary edema. Advances during the past year are highlighted below.

- One kind of white blood cell, the granulocyte, is an important part of the body's defense against infection. These cells can engulf bacteria, but can also release enzymes that may damage normal cells. Some evidence suggests that, in the presence of endotoxin, granulocytes may damage the cells that line blood vessels (endothelial cells), causing them to leak excessively.

  The effects of endotoxin on lung blood vessels in sheep with normal numbers of granulocytes were measured and the effects were measured again after the animals had been depleted of granulocytes with a drug, hydroxyurea. Endotoxin caused much less damge to lung blood vessels when there were no granulocytes. This finding implies that granulocytes in the blood are at least partly responsible for damaging lung blood vessels and suggest that drugs to prevent those cells from lodging in small lung blood vessels may prevent the lung damage that occurs with some bacterial infections.

- Investigators have found that pulmonary capillary blood volume (Vc) in human subjects during prolonged rest on their backs exhibits a slow continuous decrease. Vc was measured by the single breath carbon monoxide method, and its observed decrease in all subjects over the duration of the experiment (90 minutes) confirms a serendipitous discovery made while measuring protein equilibration by the external radioflux detection method. This new finding offers additional and independent evidence in man that the external detection of gamma-emitting tracers is capable of measuring lung events accurately, and adds a new time dimension to the redistribution of pulmonary blood volume in supine subjects. The immediate increase in central blood volume that occurs when a person lies down is dissipated over the next hour or so.

Pediatric Pulmonary Disease SCOR's

NHLBI supports seven specialized centers in pediatric pulmonary diseases which emphasize basic and clinical research on neonatal respiratory diseases, cystic fibrosis, and bronchiolitis. The following accomplishments are indicative of progress made during the past year.

- A research program is under way to attempt to discover the reasons for the unusual susceptibility of cystic fibrosis patients to pseudomonas infections of the lung. Clinically, it is nearly impossible to eradicate pseudomonas from the lungs of cystic fibrosis patients once the organisms have colonized because pseudomonas is highly resistant to most antibiotics. Speculations on the nature of this peculiar susceptibility have included the possibility that the patient's immunologic mechanisms may prolong and enhance the lung damage that occurs during such infections. One mechanism of such lung damage may involve the antibody IgE, which is traditionally associated with an intermediate hypersensitivity type of reaction in lung tissue. Sensitive methods have now been developed for examining pseudomonas-specific IgE antibody. Using this method in a preliminary study, researchers found pseudomonas-specific IgE antibodies in a significant number of blood samples from cystic fibrosis patients. This finding suggests that an antibody-mediated mechanism may be involved in the lung damage associated with pseudomonas infections in cystic fibrosis.

- The well-known resistance of the newborn to lack of oxygen is not completely understood. Newer radiographic techniques have made possible the study of this phenomenon as it relates to the brain, and they have been used to explore the effects of hypoxia in newborn animals. It appears that these animals redistribute blood flow to the brain under hypoxia circumstances in a manner that preferentially serves the metabolic needs of the "vegetative" forebrain (gray matter). This finding correlates with the clinical observation that many adult and newborn patients survive hypoxic insults (e.g., drowning) and are able to breathe and maintain heart action, but in an unconscious, or vegetative, state. It may be that these hypoxic shifts of cerebral blood flow can be manipulated with medical intervention in a manner that could protect the gray matter from hypoxic damage.

Fibrotic and Immunologic Interstitial Lung Disease SCOR's

Four SCOR's supported by NHLBI are addressing basic and clinical research topics in hypersensitivity pneumonitis, pulmonary fibrosis, and noninfectious granulomatosis, especially sarcoidosis. Examples of recent advances in these areas are given below.

- Desquamative interstitial pneumonitis (DIP) is a chronic fibrotic lung disease characterized by interstitial inflammation and fibrosis with large numbers of cells which are unusual in appearance filling the airspaces. Recent electron microscopic studies of lung tissue from patients with DIP have demonstrated that these cells are alveolar macrophages. Thus, DIP appears to represent a disease with striking hyperplasia of the macrophage population. Whether DIP represents the early inflammatory phase of conventional interstitial pneumonitis or whether it is a distinct disease entity remains controversial.

- Fetal alcohol syndrome is characterized by a broad spectrum of congenital abnormalities in the offspring of mothers who drink heavily during their pregnancies. Among these abnormalities is an inhibition of growth and collagen synthesis. Working with fetal lung fibroblast cell cultures, investigators have found that cultures treated with nonlethal levels of ethanol exhibit markedly decreased rates of synthesis of collagen, DNA, and RNA. Collagen is the major synthetic product of fibroblasts and it constitutes approximately 30 percent of total body weight. Inhibition of this macromolecular synthesis by fibroblasts may be the biochemical mechanism by which nonlethal doses of ethanol inhibit growth.

Thrombosis SCOR's

The three Thrombosis SCOR's supported by NHLBI focus on the study of processes of blood clot formation, development of clotting disorders, and methods for diagnosis. Examples of scientific advances made in 1980 are given below.

- Dose response studies utilizing normal human volunteers have established that platelets are highly sensitive to the effects of aspirin. Almost complete inactivation of prostaglandin synthetase for the lifespan of the platelet is achieved at a dose of 80 mg per day of aspirin. In fact, dosage of 160 mg of aspirin per day completely inactivates platelet cyclooxygenase. In contrast, it has been found that cyclooxygenase from human aorta and coronary arteries, as well as from a variety of cells cultured from human blood vessels, shows much less sensitivity to inactivation by aspirin. Thus it was postulated that aspirin could be administered in a dosage that would inhibit platelet prostaglandin synthesis without affecting the synthesis of the antithrombotic vascular prostaglandin, prostacyclin. In a recent randomized study of 44 patients admitted for arteriovenous shunt placement for vascular access for chronic hemodialysis, low-dose aspirin was shown to be an effective antithrombotic agent. If studies indicate efficacy of aspirin in other pathologic states, such as coronary artery disease, low doses of aspirin (160 mg per day or even less) are likely to be effective. If, indeed, small amounts of aspirin are to be used as prophylactic medication in large populations of asymptomatic individuals, the lowest possible effective dose should be used to avoid side effects.

- Considerable data from human autopsies and from experimental animal models indicate that immunologic injury of vessel walls consequent to deposition of circulating immune complexes or by mechanisms associated with graft rejection can lead to the development of arteriosclerosis. Serum sickness arteritis has a predilection for coronary arteries and spares cerebral arteries for reasons that are obscure. Such injury acts synergistically with even modest hyperlipidemia to accentuate lesion development.

  Consideration of known risk factors for cardiovascular disease indicates that cigarette smoking might provide a repetitive antigenic stimulus to the allergic smoker and, by protracted, subtle injury, induce atherosclerosis.

  Data from recent investigations suggest that cigarette smoking and, conceivably, inhalation of similar environmental antigens induce vascular injury through activation of Factor XII-dependent pathways, release of vasoactive amines mediated by anaphylactic antibodies, or the synergistic action of both mechanisms.

Clinical Trials: Validating New Knowledge

In a droll but telling observation, Sir Robert Platt wrote in 1953, "The conventional picture of the research worker is that of a rather austere man in a white coat with a background of complicated glassware. My idea of a research worker, on the other hand, is a man who brushes his teeth on the left side of his mouth only so as to use the other side as a control and see if tooth-brushing has any effect on the incidence of caries." But, regardless of one's perception of scientists or the scientific process, the bridge between development of knowledge in laboratories and clinics and application of this information in medical practice is provided by clinical trials.

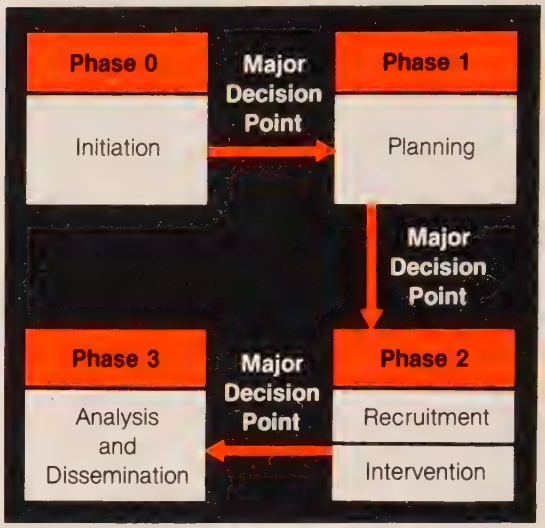
In carefully controlled settings involving human populations, NHLBI-sponsored clinical trials critically test and evaluate the effectiveness and safety of new methods to treat and prevent heart, lung, and blood diseases. In some cases trials are used to determine which of several alternative treatments already in use is the most effective.

Depending on the nature of the health care technology being tested, the trial itself may vary in size from a small study involving only a few patients to a large investigation involving thousands of patients and many health care facilities across the country. Because of the considerable resources required for large-scale clinical trials and the enormous potential impact on medical practice, the decision to undertake a particular clinical trial must be analytical and deliberate. The Institute undertakes a clinical trial only after careful study and detailed planning. In most cases, the trial is part of a logical progression of concepts as they emerge from basic science through clinical research to the points at which large-scale testing is required.

A clinical trial consists of four phases as shown in figure 13. In phase 0, the trial is conceptualized and preliminary planning takes place; phase 1 involves the detailed planning of the trial and finalizing the protocol and operational procedures; phase 2, the actual conduct of the trial, involves patient recruitment, intervention, followup activities, and ongoing analysis of results; phase 3 encompasses the final analysis of the trial results and their dissemination.

At each decision point within and between phases of a clinical trial, a number of groups review the progress of the trial and attempt to balance a set of often disparate factors. These decision factors generally fall into four major categories: the state of the science related to the trial; the feasibility of the effort based on the state of knowledge and available resources; the potential impact of the trial on health care and on research; and various ethical considerations inherent in the use of human subjects. Through experience the Institute has found that the phased approach to management allows careful consideration of each of these decision factors at stages in the trial at which full resources have not yet been fully committed. Thus, the process allows the changing state of scientific knowledge and the health care system to influence these projects so that they can be developed and carried out to best serve both science and society.

Figure 13.
Clinical Trial Decision Process



Two major clinical trials completed by the Institute during the past year illustrate the important role of such studies in evaluating the validity, efficacy, and safety of different preventive and therapeutic regimens. Results of the trials were markedly different in terms of the concluded value of the regimens under investigation—the effect of aspirin on morbidity and mortality in survivors of myocardial infarction and the effect of "stepped-care" hypertension control on total mortality—but both studies provide invaluable information that may affect the lives and health of millions of Americans suffering from cardiovascular diseases. These two trials are described below. (A third clinical trial completed during the past year was the Nocturnal Oxygen Therapy Study, which indicated that 12-hour nocturnal oxygen therapy is not as beneficial as continuous oxygen therapy in extending life in patients with severe respiratory impairment. This study is described in greater detail in chapter 5.)

Aspirin Myocardial Infarction Study

Preliminary evidence that regular administration of aspirin may be of benefit to patients with known

coronary heart disease has come from several sources. One collaborative drug study compared the prior use of aspirin by hospitalized patients with a discharge diagnosis of myocardial infarction to its use by patients with other diagnoses. Data showed a considerably lower use of aspirin among the MI group relative to the other group. Another study, a prospective, randomized, double-blind trial, compared men with a recent MI for whom either aspirin or placebo was prescribed; results showed an overall mortality trend in favor of aspirin, but were not statistically significant. A similar trial, the NHLBI-sponsored Coronary Drug Project Aspirin Study, prescribed aspirin or placebo to men who had survived one or more MI's, but all subjects in the aspirin study were remote from their MI and had been on medication to lower blood lipids for several years before entering the aspirin study. The mortality in the aspirin-treated group was 30 percent lower than in the placebo group, but again, the difference was not statistically significant. Nevertheless, this pilot trial demonstrated the feasibility of conducting a larger, more rigorous study.

In addition to these clinical studies, there is considerable evidence that thrombosis plays a major role in the late stages of coronary artery occlusion. Platelet aggregation is a large component in the formation of arterial thrombi. Theoretically, an agent that prevents the aggregation of platelets might be of value in people with coronary artery disease. Aspirin, in small doses, inhibits platelet aggregation for prolonged periods of time and therefore might be expected to prevent or retard the occlusion of coronary arteries. This would be reflected in a decrease in the incidence of MI and a decrease in mortality due to coronary artery disease.

On the basis of these encouraging but inconclusive clinical findings and the antiplatelet properties of aspirin, the NHLBI initiated the Aspirin Myocardial Infarction Study in 1975 as a more definitive controlled trial of the benefit of aspirin in reducing mortality or in decreasing further risk in patients who had suffered at least one MI.

Over a 13-month period, 4,524 persons between the ages of 30 and 69 who had sustained an MI an average of 25 months earlier were randomized to either 1 g of aspirin per day or placebo. High levels of patient compliance to study protocol were indicated by various measures. Recently published results showed that total mortality during the entire followup period—from 3 to 4 years—was 10.8 percent in the aspirin group and 9.7 percent in the placebo group. All patients were followed at least 3 years, and for this period total mortality was 9.6 percent in the aspirin group and 8.8 percent in the placebo group. The percentage of definite nonfatal MI was 8.1 percent in the placebo group and 6.3 percent in the aspirin group. Coronary incidence (coronary heart disease mortality or definite nonfatal MI) was 14.1 percent in the aspirin group and 14.8 percent in the placebo group. Symptoms suggestive of peptic ulcer, gastritis, or erosion of gastric mucosa (untoward side effects) occurred in 23.7 percent of the aspirin group and 14.9 percent of the placebo group.

Results of the trial, the largest completed and published investigation of aspirin in the post-MI population, reveal no benefit from aspirin. Data indicate that aspirin perhaps is helpful in reducing the frequency of nonfatal MI but leads to an increased incidence of side effects. They clearly indicate that the regular administration of aspirin in this dose does not reduce 3-year mortality in patients with a history of MI, the primary endpoint. On the basis of the AMIS results, aspirin is not recommended for routine use in patients who have survived a myocardial infarction.

Hypertension Detection and Follow-up Program

The HDFP, a multicenter clinical trial, was carried out concurrently with the National High Blood Pressure Education Program. The questions it set out to answer in 1972 were the following:

- Can treatment of hypertension be shown to be beneficial in reducing morbidity or mortality in patients with mild hypertension (diastolic pressure 90 to 104 mm Hg) for whom it has been suggested that drug side effects might outweigh benefits?
- Can all patients in the community who are found to have high blood pressure be placed on treatment and maintained on treatment?
- Is hypertension control as effective in younger men, in women, and in minority groups as in the older, male, predominantly white VA population in whom definite beneficial results had been shown at higher elevations of blood pressure?
- Can treatment of high blood pressure reduce coronary heart disease deaths, especially deaths from acute myocardial infarction?

Fourteen clinical centers in the United States were competitively selected to participate in the study. After the screening of 159,000 people aged 30 to 69 in the defined populations served by these centers, 10,940 people with confirmed hypertension were enrolled in the study. Half of the patients, including those with mild hypertension, received vigorous stepped-care treatment at the 14 clinical centers. Patients received drug therapy, increased in a stepwise fashion if necessary to avoid discouragement by side effects, until they achieved and maintained reduction of diastolic blood pressure to or below set goals.

The second half of the study participants were assigned to the referred-care group, in which patients were referred to the existing medical care

system in the community ("standard of care"). These referred-care patients were urged to continue their treatment and were seen by HDFP personnel several times during the 5 years of the study. If severe hypertension was found, special steps were taken to ensure appropriate care.

Results of the study demonstrate that people with high blood pressure, even those with "mild" hypertension, who undergo systematic care with blood pressure control goals will live considerably longer than those who receive routine care or no care at all. Persons in the stepped-care group showed a 17 percent reduction in 5-year all-cause mortality compared with those receiving referred-care, indicating that tens of thousands of Americans with high blood pressure are probably now dying at an earlier age than they should. Treatment was effective in lowering blood pressure for all groups regardless of age, sex, or race.

Of the approximately 25 million Americans with so-called mild hypertension, millions are not being treated because, until completion of the HDFP, there was no clear scientific proof of the benefits of treating them. This study clearly demonstrated that systematic effective treatment of all mild hypertensive patients—rather than simply to the variable extent typically practiced—may reduce the incidence of premature deaths by 20 percent. Moreover, among mild hypertensives on stepped care, death rates from all cardiovascular causes were 26 percent lower, and from noncardiovascular causes 12.5 percent lower, than among patients on referred care. And, most important, the stepped-care group's mortality from stroke and acute myocardial infarction was about 45 percent lower than that of the referred-care group.

The HDFP will have a final cost of nearly $70 million. However, if the lessons learned from the trial are applied to health care delivery, a return well into the billions of dollars each year will be realized as the morbidity and mortality associated with hypertension decrease.

Ongoing Clinical Trials

Table 7 lists, by sponsoring Division, NHLBI's ongoing clinical trials and indicates the current status of each. The following paragraphs briefly highlight the Institute's largest clinical trials now under way and indicate the potential savings, in dollars and in lives, that can be realized by the application of knowledge gained in these trials.

Two clinical trials currently sponsored by NHLBI are aimed at primary prevention of coronary heart disease. The *Coronary Primary Prevention Trial* (CPPT) is designed to determine whether drug therapy to reduce serum cholesterol levels will significantly reduce the rate of atherosclerotic heart disease in a group of otherwise healthy men who have high levels of cholesterol. The *Multiple Risk Factor Intervention Trial* (MRFIT) is designed to determine whether a special intervention program that simultaneously lowers serum cholesterol and blood pressure and reduces or eliminates cigarette smoking will significantly reduce coronary heart disease mortality for men at high risk.

Both of these trials are expected to yield tremendous benefits. If these approaches can lower the death rate for arteriosclerosis by as little as 1 percent, the annual reduction in costs due to cardiovascular disease could amount to over $500 million.

Coronary artery surgery and the diagnostic procedures that precede it are very costly in both money and manpower resources. The estimated average cost for each surgical procedure of this type is $15,000, and up to 100,000 such procedures are performed annually in the United States. The *Coronary Artery Surgery Study* is comparing the effectiveness of coronary artery surgery to that of medical (pharmacologic) management in patients with coronary artery disease. The study maintains a registry of patients undergoing coronary arteriography whether these patients are managed operatively or medically.

Each year an estimated 1.25 million people suffer heart attacks and some 60 percent die. Two current NHLBI clinical trials are examining therapies to improve a patient's prognosis following heart attacks. The *Beta Blocker Heart Attack Trial* is testing whether the administration of beta-blocking drugs will reduce mortality in persons who have suffered a myocardial infarction. The *Multicenter Investigation of the Limitation of Infarct Size* is testing means designed to limit the extent of acute damage to heart tissue. Less damage should mean a better prognosis for patients with myocardial infarction. The outcomes of both these trials should allow a reduction in heart attack mortality and a consequent reduction in the costs of care and socioeconomic losses from early death.

Respiratory distress syndrome is among the leading causes of impaired function and death in the newborn. Each year about 50,000 cases of neonatal respiratory distress syndrome occur. The *Neonatal Respiratory Distress Syndrome* trial is evaluating the effect of corticosteroids on the incidence of RDS. If this prenatal preventive measure proves valid, it could significantly reduce the estimated annual treatment cost of $250 million in the United States alone.

Intermittent positive pressure breathing is a common adjunct therapy for patients with chronic obstructive lung disease. Its efficacy, however, has yet to be determined. The *Intermittent Positive Pressure Breathing* trial is evaluating the efficacy of long-term IPPB. Annual treatment costs for at-home IPPB are estimated at more than $30 million. This trial will determine the effectiveness of this expensive yet unproven treatment for ambulatory patients.

Table 7.
Ongoing NHLBI Clinical Trials

Division of Heart and Vascular Diseases		
Coronary Drug Project (CDP): Secondary prevention of coronary heart disease with cholesterol-lowering drugs.	8,341 subjects followed for 5 to 8-½ years at 53 clinics.	Initiated in 1965. Recruitment and Intervention completed in 1975. Now in Analysis and Dissemination. Phase 3.
Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT): Primary prevention of coronary heart disease in hypercholesterolemic patients with the cholesterol-lowering drug cholestyramine.	3,810 subjects followed for 7 years at 12 clinics.	Initiated in 1973. Now in the Intervention stage of Phase 2.
Multiple Risk Factor Intervention Trial (MRFIT): Primary prevention of coronary heart disease by lowering serum cholesterol, reducing blood pressure, and reducing or eliminating cigarette smoking.	12,866 subjects followed for 6 years at 20 clinics.	Initiated in 1972. Now in the Intervention stage of Phase 2.
Hypertension Detection and Follow-up Program (HDFP): Evaluation of hypertension control to reduce total mortality.	10,940 subjects followed for 5 to 6-1/3 years at 14 clinics.	Initiated in 1971. Now in Analysis and Dissemination. Phase 3.
Unstable Angina Pectoris Trial: Secondary prevention of coronary heart disease by coronary artery bypass surgery or medical management in patients with unstable angina pectoris.	288 subjects followed for 9 years at 9 clinics.	Initiated in 1972. Now in Analysis and Dissemination. Phase 3.
Coronary Artery Surgery Study (CASS): Treatment of coronary heart disease by artery bypass surgery or medical management in patients with stable angina pectoris.	780 subjects have been entered into this trial, which has a goal of 800 randomized patients to be followed for at least 4 years at 10 clinics. The study also includes a registry of 24,188 patients referred for coronary arteriography with a goal of 25,000 patients at 15 clinics.	Initiated in 1973. Now in Intervention. Phase 2.
Program on Surgical Control of Hyperlipidemias (POSCH): Reduction in mortality in survivors of myocardial infarction by partial ileo bypass surgery.	Over 300 subjects have been recruited into this trial, which has a goal of 1,000 subjects. Patients are to be followed for a minimum of 5 years at 4 clinics.	Initiated in 1973. Now in Recruitment and Intervention. Phase 2.
Aspirin Myocardial Infarction Study (AMIS): Reduction in mortality in survivors of myocardial infarction by use of the drug aspirin.	4,524 subjects followed for 3 to 4 years at 40 clinics.	Initiated in 1975. Now in Analysis and Dissemination. Phase 3.

Table 7.
Ongoing NHLBI Clinical Trials (Continued)

Division of Heart and Vascular Diseases		
Beta-Blocker Heart Attack Trial (BHAT): Reduction in mortality in survivors of myocardial infarction with the drug propranolol (a beta-blocker).	3,847 subjects to be followed for up to 4 years at 31 clinics.	Initiated in 1977. Now in Intervention. Phase 2.
Multicenter Investigation of Limitation of Infarct Size (MILIS): Treatment of myocardial infarction with the drugs propranolol and/or hyaluronidase.	1,500 patients will be followed for 6 months in 5 clinics.	Initiated in 1977. Now in Recruitment and Intervention. Phase 2.
Treatment of Hypertension: Primary prevention of cardiovascular morbidity and mortality by drug treatment of hypertension with chlorothiazide plus *Rauwolfia serpentina*.	389 subjects followed for up to 9 years at 6 clinics.	Initiated in 1966. Recruitment and Intervention completed in 1976. Now in Analysis and Dissemination. Phase 3.
Management of Patent Ductus in Premature Infants: Comparison of treatment of patent ductus arteriosis with the drug indomethacin, or with surgery, and conventional medical therapy.	400 babies to be followed for 1 year at 12 clinics.	Initiated in 1978. Now in Recruitment and Intervention. Phase 2.
Systolic Hypertension in the Elderly Program (SHEP): Prevention of stroke with standard antihypertensive agents.	500 subjects to be followed at 5 clinics.	Now in Planning, Phase 1, of a pilot study to last 5 years.
Division of Lung Diseases		
Neonatal Respiratory Distress Syndrome: Primary prevention of neonatal respiratory distress syndrome by administration of corticosteroids before birth.	800 subjects to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Analysis and Dissemination. Phase 3.
Intermittent Positive Pressure Breathing (IPPB): Treatment of chronic obstructive pulmonary disease with intermittent positive pressure breathing compared with powered nebulizer.	About 1,000 subjects to be followed for 3 years in 5 clinics.	Initiated in 1976. Now in Intervention. Phase 2.
Nocturnal Oxygen Therapy: Treatment of chronic hypoxic lung disease with 12-hour oxygen therapy compared to continuous low-flow oxygen therapy.	200 subjects followed for up to 30 months at 6 clinics.	Initiated in 1976. Recruitment and Intervention completed in 1979. Now in Analysis and Dissemination. Phase 3.
Extracorporeal Support for Respiratory Insufficiency (ECMO): Treatment of acute respiratory failure with an extracorporeal membrane oxygenator.	90 subjects followed for at least 5 days in 9 clinics.	Initiated in 1974. Recruitment and Intervention completed in 1977. Now in Analysis and Dissemination. Phase 3.

Table 7.
Ongoing NHLBI Clinical Trials (Continued)

Division of Blood Diseases and Resources		
Granulocyte Transfusion Study: Primary prevention and treatment of infection in patients undergoing chemotherapy for leukemia.	141 subjects followed for 3 years in 4 clinics.	Initiated in 1976. Recruitment and Intervention ended in February 1980. Now in Analysis and Dissemination. Phase 3.
Cooperative Study of Factor VIII Inhibitors: Factor IX treatment of persons with hemophilia A and inhibitors to Factor VIII.	70 subjects followed for varying lengths of time in 10 clinics.	Initiated in 1978. Intervention completed in late 1979. Now in Analysis and Dissemination. Phase 3.
Division of Intramural Research		
NHLBI Type II Coronary Intervention Study: Evaluation of coronary artery disease regression from cholestyramine (a lipid-lowering drug) in people with Type II hyperlipidemia.	143 subjects followed for 5 years at 1 clinic.	Initiated in 1971. Now in Intervention stage of Phase 2.
Diffuse Fibrotic Lung Disease: Treatment of idiopathic pulmonary fibrosis by azathioprine versus prednisone.	Approximately 150 subjects followed for up to 1 year in 1 clinic.	Initiated in 1974. Now in Intervention stage of Phase 2.
Evaluation of Subcutaneous Desferrioxamine as Treatment for Transfusional Hemochromatosis: Treatment of iron-overload with the agent desferrioxamine and ascorbic acid.	50 to 65 eligible subjects followed for up to 5 years in 2 clinics.	Initiated in 1973. Now in Recruitment and Intervention. Phase 2.

Future Clinical Trials

As many as 15 million citizens over 60 years of age have hypertension, and while hypertension treatment is widely recommended, its net efficacy has not yet been validated for the elderly. Of particular interest is systolic hypertension, associated with hardened arteries and particularly in those of advanced years. Here also the benefits in reducing stroke and heart disease may be substantial, but such treatment needs to be assessed because possible side effects may be significant. A proposed clinical trial, the *Systolic Hypertension in the Elderly Program* (SHEP), is actively planned to determine whether treatment of isolated systolic hypertension in patients over 60 will reduce the incidence of stroke, myocardial infarction, congestive heart failure, and renal insufficiency.

In the Nation as a whole, more than 35 million persons have definite hypertension. Hypertension control now relies primarily on drug treatment, which may range in cost from $60 to over $600 annually for each patient, depending on the prescribed regimen. The *Effect of Dietary Modification in Blood Pressure Control* trial is proposed to determine whether restrictions on salt intake, increase in potassium intake, and loss of weight will reduce the need for hypertension therapy with drugs. The trial could ultimately reduce both the potential side effects of current drug treatment and overall health care costs.

Each year some 500,000 patients survive a heart attack but face at least a twofold increase in risk of cardiovascular death. Recent clinical trials indicate that the first year following myocardial infarction, particularly the first 3 months, may be a critical period in which administration of platelet-active drugs may be most effective in the prevention of sudden death. A potential clinical trial is being considered to evaluate the effect of various platelet-active drugs on mortality and morbidity during the first 3 months after myocardial infarction.

6

Resource Allocations:

Sustaining the Pledge of Research

Federal concern for the advancement of medicine was translated into financial support a century ago, when in 1879 the National Board of Health was created by law. This first organized, comprehensive, national medical research effort of the government pales in comparison with today's National Institutes of Health, one of the world's foremost and prestigious biomedical research centers. A prime example of this increasing Federal commitment to research is provided by NHLBI. Since 1972, Congress has expanded the Institute's mandate in a steady progression, giving NHLBI new responsibilities in the areas of lung diseases, blood diseases, blood resources, sickle cell disease, clinical trials, research and demonstration centers, prevention, education, and control, and high blood pressure education.

As its continuing record of research accomplishments attests, the Institute has fulfilled its pledge to keep in step with the rapid march of scientific progress. Nevertheless, within the Institute there remains a significant need to fully address the problems identified in the National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program. As a result, the Institute must develop creative ways to ensure that the ever-increasing number of scientifically worthy and Program-relevant research proposals submitted to NHLBI each year are given the opportunity for adequate funding.

Fiscal Resources

For NHLBI to carry out its mandated responsibilities, Institute resources must increase each year to match both inflation and advances in the sophistication of scientific technologies. In 1972, the year in which the National Heart, Blood Vessel, Lung, and Blood Act was passed, the Institute's appropriations amounted to $232.6 million. By 1981, NHLBI projected appropriations had risen to $560.3 million. Adjusting for inflation expressed in terms of constant 1972 dollars (using the biomedical price deflator), this amount corresponds to only $280.2 million. Moreover, medical care costs have risen considerably faster than the overall cost of living, and this factor is also reflected in the increasing cost of medical research.

Similarly, the Institute's share of total NIH research funds has remained essentially constant, fluctuating between 16 and 17 percent since 1970.

The inability of NHLBI to fund many meritorious research projects is a problem shared by other Institutes in an era of responsible Federal fiscal restraint. The number of competing research project grant applications submitted and reviewed by NHLBI has grown substantially, from 1,100 in 1971 to 2,193 in 1980 (table 8). Much of this increase can be attributed to the Institute's expanded mandate, but it is also a reflection of the growth in research opportunities. Over these years the number of grants approved for funding has increased as well, but because of the limited funds available, the fraction of approved grants which could actually be awarded has diminished significantly: from 61 percent in 1971, to 27 percent in 1980.

As shown in table 9, direct costs associated with a sample of selected research grants have increased substantially, rising from $72.0 million in 1970 to $197.6 million in 1980. However, the indirect costs accompanying these grant awards have risen even more steeply—from $20.0 million in 1971 to $79.5 million in 1980. As a result, nearly 29 cents of each dollar spent on research grants is absorbed by indirect costs.

In any consideration of the Institute's current and planned resource allocations, it should be noted that almost all projects supported by the Institute represent multiyear awards. Thus, in any given year a large fraction of the Institute's budget is required to continue the activities already ongoing and committed. Only a small fraction is available for the competitive renewal of existing projects and the initiation of new activities.

All of these factors require that NHLBI program planning and implementation activities carefully consider competing priorities. With this perspective, NHLBI bases its projection of resource needs on a critical review of the state of the science, future research needs and opportunities, and

Table 8.
Trends in NHLBI Investigator-Initiated Research: Competing Research Project Grants*

Year	Reviewed	Approved	Total Eligible**	Awarded	Percentage of Eligible Grants Awarded
1971	1,100	718	731	446	61
1972	1,167	773	944	492	52
1973	1,279	933	1,104	426	39
1974	1,501	1,117	1,191	662	56
1975	1,531	1,137	1,444	629	44
1976	1,615	1,192	1,492	707	50
1977	2,180	1,600	1,970	729	37
1978	2,129	1,595	1,985	759	38
1979	2,239	1,679	2,138	942	44
1980	2,193	1,738	2,158	589	27

*Includes research project grant applications (R01's, P01's, R23's — types 1, 2, 3, and 9).
**Includes approved but unfunded grants still active from previous year.
SOURCE: Division of Research Grants.

Table 9.
Growth of Indirect Cost Rates of Research Grants,* Fiscal Years 1972-1980

Fiscal Year	Direct	Indirect	Indirect Cost as a Percentage of Total Cost	Total Cost
1971	$ 72,020,575	$20,021,425	21.8	$ 92,042,000
1972	81,350,199	25,035,497	23.5	106,385,696
1973	86,539,991	27,674,325	24.2	114,214,316
1974	109,691,890	37,797,863	25.6	147,489,753
1975	101,970,760	36,288,184	26.2	138,258,944
1976	124,915,900	44,436,926	26.4	168,352,826
1977	142,110,745	51,021,715	26.4	193,132,460
1978	157,696,047	59,122,100	27.3	216,818,147
1979	189,722,315	73,565,604	27.9	263,287,919
1980	197,639,614	79,484,057	28.7	277,123,671

*Includes regular project grants, program grants, young investigator awards, and sickle cell centers. Excludes research career programs, cooperative clinical research, scientific evaluation and conference grants, research and demonstration centers, and SCOR's.

specific estimates of the resources needed to support both ongoing commitments and new initiatives. This review process involves both scientific and administrative assessment of the fiscal resources, personnel, and time required to sustain progress and accomplish National Program objectives.

Resource allocations represent resources needed to carry out the program activities in all areas of the Institute. In accordance with legislative requirements, at least 15 percent of the fiscal resources must be allocated for diseases of the lung, and at least 15 percent for blood diseases and blood resources.

Although restraint and austerity in many areas of the economy are appropriate, the Institute believes that careful expansion of research directed against diseases of the heart, lung, and blood is indicated at this time. Health costs continue to rise each year, and they can be controlled by lessening the need for health care and developing new approaches and techniques—particularly those that lead to prevention of disease—that will decrease health care delivery costs.

The rationale for the projected resource allocations presented in table 10 can be found in detail in chapter 3, Program Goals and Planned Activities. The major issues addressed by projects this year are summarized below.

- **Investigator-Initiated Research Program**—The current high rate of inflation—affecting every category of the budget, from salaries and supplies to maintenance of apparatus and overhead—has limited the impact of the 1980 research dollar. The Institute's commitment to a strong investigator-initiated research program is reflected in the budget projection in each program area. Table 10 estimates funds needed to meet these increasing research needs.
- **National Research and Demonstration Centers**—The projected budget for research and demonstration centers provides for another major competition in FY 1982. These centers will continue to hasten the process by which research results are validated and applied to improve community health care.
- **Prevention, Education, and Control Programs**—New Institute mandates to identify cardiovascular risk factors and the effect of their modification on health are reflected in the increased projections for prevention, education, and control activities.
- **Training**—The increase in training dollars in this year's projections reflects the Institute's commitment to reverse the steady decline in the number of physician investigators during the past 8 years. The Clinical Investigator Award was implemented in FY 1980 in an effort to stabilize this downward trend and create a basis for steady increases in the number of new trainees.
- **Intramural Research**—As the NIH Ambulatory Care Facility construction phase nears completion, the intramural research budget projections reflect a moderate increase to meet additional staffing requirements associated with facility operation.

NHLBI Staff Allocation Plan

Since the enactment of the Institute's new legislative mandate in 1972, the NHLBI has suffered a personnel shortage. Many new programs, especially those involving clinical trials and targeted activities, require a high ratio of staff manpower dollars. To operate the National Program effectively, the NHLBI needs additional staff at all personnel levels—middle and senior professionals as

Table 10.
Projected Resource Allocation* for the National Heart, Blood Vessel, Lung, and Blood Diseases and Blood Resources Program, Fiscal Years 1982-1986 (Dollars in Millions)**

	1982	1983	1984	1985	1986
Extramural Research Programs					
Heart and Vascular Diseases	$279.2	$298.1	$310.4	$331.4	$354.5
Lung Diseases	72.6	82.1	89.9	92.7	99.0
Blood Diseases and Resources	74.6	84.6	96.2	99.8	106.7
National Research and Demonstration Centers	6.2	7.0	12.0	14.0	16.0
Prevention, Education, and Control Programs	33.1	40.3	42.8	45.7	42.1
Training	29.5	35.5	37.6	39.8	42.2
Construction	0	0	0	0	0
Total Extramural Research Programs	$495.2	$547.6	$588.9	$623.4	$666.5
Intramural Research	49.7	51.8	52.9	53.9	57.6
Direct Operations and Program Management	34.7	41.4	43.9	46.5	49.2
TOTAL	$579.6	$640.8	$685.7	$723.8	$773.3

*These tabulations give the primary thrust of activities, even though the activities generally involve more than one subprogram.

**Based on NHLBI professional estimates and does not reflect competing priorities within the Department or the Administration.

Figure 14.
Percentage of Change in Obligations and Employment, 1972 to 1980

well as support staff. The direction and administration of new programs of the National Institutes of Health, such as disease prevention, control, and education and comprehensive centers, as well as review and evaluation, require additional personnel with knowledge and skills different from those previously available within the Institute. Because these programs require substantially greater staff involvement than do regular grants programs, manpower needs are particularly pressing.

To initiate these extensive new programs with currently available manpower resources, the Institute has conserved manpower by reorganization and centralization of special activities, adoption of dual organizational functions by a number of top-level personnel, and the transfer of staff from established ongoing programs to meet new program needs.

Figure 14 compares the percentage of increase in NHLBI obligations to the percentage of increase in employment between 1972 and 1980.

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